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# THE FUNCTIONS OF THE NERVES IN LUNGS AND THORACIC WALL<sup>1</sup>

CECIL K. DRINKER<sup>2</sup>

As knowledge of the physiology of breathing has accumulated, and the increase in the past ten years, accelerated by the many practical problems arising from the war, has been very rapid, it has been my experience that our realization of the complexity of the process has been vastly augmented.

Nothing is of such fundamental importance to living creatures as a free and constant supply of oxygen. The single source of this indispensable element is the air. It is not surprising that, as knowledge advances, it is found that more and more mechanisms in the body possess the means of asserting their need for oxygen. In some cases, this need is far greater than in others. Some of the cells of the cerebral cortex, for example, are damaged irreversibly by seven to ten minutes of complete anoxia. In other regions, such as the intestines, over half an hour of deprivation of oxygen may fail to cause permanent harm, though for a time the tissue may be quite abnormal.

There is a center for breathing, a bilateral collection of nerve cells in the lower part of the pons and in the upper two-thirds of the medulla. This is true for man and for the dog and cat. The cells in this grey reticulum are connected synaptically, *i.e.*, their fibers are not continuous. The nerve impulses pass from one fiber to another by the peculiar contact arrangement which Foster and Sherrington (1) called the synapse. Sherrington (2), in his lectures on the integrative action of the nervous system, one of the great classics of modern physiology, showed many of the consequences to nerve impulses transmitted through contacts, *i.e.*, with an interface between the conducting fibers, as contrasted with conduction along an unbroken axone. He did not realize how much further his conception would progress as the newer methods of physical chemistry began to be used in analyzing phenomena mediated through nerves. For example, all of the newer studies of the transmission of nerve impulses from one nerve fiber to another, and from the ending of the fiber to the muscle or gland cell controlled by it, depend upon the existence of interfaces. At this site chemical and physical changes can occur without affecting the size or character of the impulse conducted by the axone.

The physiology of breathing owes much of its complexity to the fact that man has developed through a vast series of simple animals, living first in water, then partially in water, and only in comparatively recent years upon the land alone. In this evolution, the essentials of the forsaken water existence have been taken along in the body fluids. When life first began, the atmosphere was heavily loaded with carbon dioxide, and the solubility of this compound in water assured

<sup>1</sup> Presented in a postgraduate course in thoracic diseases sponsored by the American Trudeau Society, in cooperation with Duke University School of Medicine and University of North Carolina School of Medicine, at Durham and Chapel Hill, North Carolina, March 22-27, 1948.

<sup>2</sup> Chestnut Hill, Massachusetts.

the necessity of living in an atmosphere very rich in  $\text{CO}_2$ . Carbon dioxide is vitally necessary to us, and is a constant excretory product of all living creatures, who must have oxygen to utilize the food they assimilate. It is not surprising to find that mammalian blood in land animals carries about 48 cc. of carbon dioxide combined within it in various ways. Of this amount, at sea level, only 3 cc. are dissolved in the plasma. Ten to 15 cc. are combined with the hemoglobin of the red cells, and the rest is carried as bicarbonate in relatively fixed condition. Yet even this last carbon dioxide, released very slowly and inadequately from bicarbonate *in vacuo*, is liberated freely and rapidly through the action of an enzyme, carbonic anhydrase, found in the erythrocytes. Land-dwelling man is thus not so far removed from his carboniferous forbears as may seem to be the case; and it is not surprising that so diffusible a gas as carbon dioxide takes part in stimulating breathing. At the same time, it has been shown that, if the breathing of a mammal is made to depend solely upon carbon dioxide stimulation of the respiratory center by section of all the afferent nerves to this dominate collection of nerve cells, breathing becomes incoördinated and the ability to increase and decrease ventilation smoothly and effectively is lost. Under such circumstances, the land-dwelling mammal becomes as sluggish and helpless as was his remote ancestor, who lived in the carbon dioxide-rich sea or upon the moist shores where the atmospheric carbon dioxide was extremely high.

These facts make it essential to examine the effects of nerves on breathing. The information thus gained has obvious place in understanding what occurs in inflammatory diseases of the lungs, such as pulmonary tuberculosis. The lungs contain nothing reactive to nerve impulses except smooth muscle in the bronchioles and blood vessels, and the glands found in the bronchial epithelium. Whether ciliary action, so important for movement of bronchial secretion, is under extrinsic nervous control is not known. In all probability, ciliary action is dependent on chemical changes in the blood and on substances applied directly. Anesthetics, such as chloroform, and sedatives depress ciliary movement and hence delay bronchial excretion. Small amounts of ether, ethylene, and alcohol apparently stimulate ciliary action (3). The subject is of considerable practical importance and merits more study than it has received.

The lung tissue contains a very large amount of smooth muscle, not only in the bronchi, bronchioles, and blood vessels, but also in the pleura. This smooth muscle is particularly prominent in the guinea pig (4), and probably accounts for the extreme sensitivity of this animal to anaphylaxis as expressed in lung phenomena. While smooth muscle in the pleura is not so prominent in man, it is present as extensions from lymphatics and blood vessels, and the sensitivity of man to anaphylactic shock, as evinced through the lungs, is second only to the guinea pig.

The lungs of all mammals possess a huge margin of safety—that is, they are large enough to provide oxygen while at rest and again during the most severe muscular exercise. It deserves comment that the ability of the lungs to operate at very different size is a characteristic of organs containing a large amount of smooth muscle and elastic tissue.

The nerves of the lungs are both afferent and efferent, and arise from the vagi and from the sympathetic or thoracic division of the autonomic nervous system. Larsell (5) found vasomotor nerves in the pleura distributed along branches of the pulmonary artery, and also larger fibers ending near the pleural surface. The latter fibers are possibly afferent in function (6).

The lung nerves with which we are most familiar are the vagal and sympathetic fibers ending in the bronchi, bronchioles, atria, and blood vessels. Each lung receives an equal supply from each source, and, in addition, the bronchial walls contain many ganglion cells with fibers arranged as a sort of nerve net, not unlike the plexuses of Auerbach and Meissner in the intestine. The function of these intrinsic nerves is not known, but certainly their presence makes complete denervation of the lungs quite impossible.

The peculiar gelatinous secretion produced by asthmatic patients and the more watery mucoid secretion familiar in pulmonary inflammation are formed by cells in the bronchial mucous membrane plus a protein-containing transudate from the capillaries in the bronchi. It may well be that swelling of the bronchial mucosa and active secretion from the bronchial glands are under nervous control. No one has been able to demonstrate this, however, though the fact of abnormal secretion is familiar enough clinically (7, 8).

In connection with swelling and hyperemia of the bronchial mucous membrane, it must be remembered that the bronchial arteries are typically systemic vessels. They follow the bronchi and branch into diffuse capillary nets in the tunica propria of the bronchioli. These capillaries end before the alveoli are reached and are not concerned with respiratory exchange. At the end of the bronchiolus, they join capillaries from the pulmonary artery. True bronchial veins are found at the hilum of the lung, where they deliver their contents to one of the azygos or intercostal veins. Anastomoses between the pulmonary arterioles and bronchial arterioles apparently do not exist. This arrangement is fortunate, for the higher pressure in the bronchial arterioles would give these vessels a commanding position in the delivery of blood to the alveoli and, as their blood is arterial, nothing physiological would be accomplished. Capillary anastomoses between the two circulations mean simply the mixing of systemic venous blood and that from the bronchioles, with resultant oxygenation of the entire supply.

It is also apparently true that the vasa vasorum of the pulmonary artery are derived from the bronchial arteries.

Wounds of the larger branches of the bronchial arteries, owing to the high pressure of the blood within them, are very serious and may result in fatal hemorrhage or in a dissecting hemorrhagic infarction extending to the pleural surface.

In summary, what one must remember is that, in addition to the low pressure pulmonary circulation, the lungs possess an extensive systemic pressure circulation capable of all the reactions seen in systemic arterioles and capillaries all over the body. Thus, if bronchial irritation occurs, dilatation of arterioles and capillaries with increased leakage and swelling of the tissues may be expected. Such familiar vascular phenomena are now spoken of as reactive hyperemia, and are certainly of major importance in dealing with infection; but no one can say



whether the vastly larger pulmonary circulation is capable of any such reaction. Indeed, aside from the facts that in abnormal conditions in the lung, such as are found in bronchopneumonia, the arterioles and capillaries in the affected region are possibly dilated and are certainly hyperpermeable, little is known about the reactivity of the finest branches of the pulmonary artery.

#### THE VAGUS NERVES

Figure 1 is a diagram of vagus and sympathetic fibers as they form the posterior pulmonary plexus and are distributed to the lungs (8). There seems little doubt

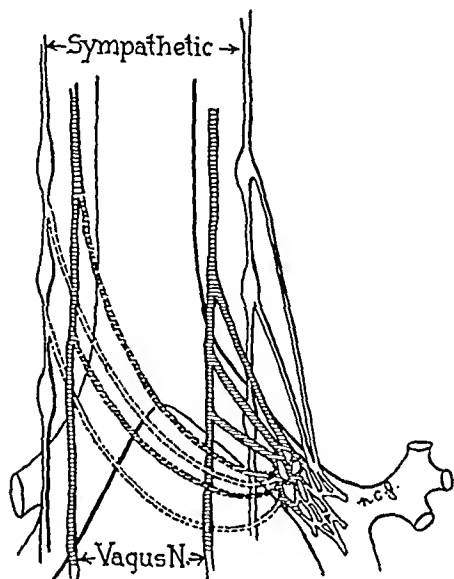


FIG. 1.

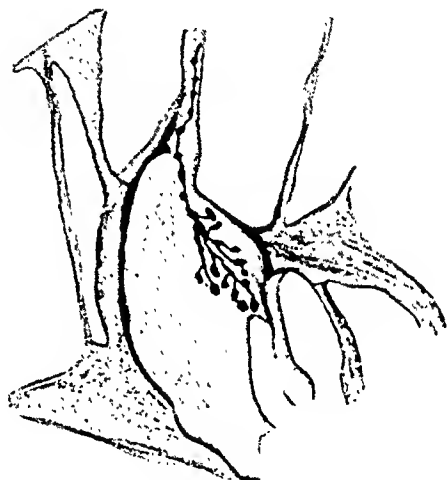


FIG. 2.

FIG. 1. Schematic representation of the participation of both the sympathetic and the vagus fibers from the same side and from the opposite side in the formation of the posterior pulmonary plexus (according to Braeueker's experiments). From Phillips, E. W., and Scott, W. J. M., *Arch. Surg.*, 1929, 19, 1430.

FIG. 2. Free nerve ending in wall of atrium. From a child eight months old.  $\times 546$ . From Larsell, O., and Dow, R. S., *Am. J. Anat.*, 1933, 52, 139.

that both vagus and sympathetic fibers are afferent and efferent. The difficulty in unraveling the functions of the two systems resides in the task of separating the fibers for functional analysis.

There is no doubt that stimulation of the distal end of one vagus results in constriction of the larger bronchi and bronchioles, most pronounced on the side stimulated, but not absolutely limited to it. Furthermore, after vagal section, paralytic dilatation of bronchioles occurs, but is not persistent.

The efferent vagal fibers distributed below the larynx are constrictor for the bronchial and bronchiolar musculature, and possibly activate the bronchial glands. None of these functions is actually respiratory, as neither set of endings takes part in the respiratory act, although both may modify it seriously and do so under pathological conditions.

The vagal respiratory impulses which take part in controlling breathing are afferent. They have their origin in nerve endings in the most distensible part of the alveolus, *i.e.*, the walls of the alveolar ducts and atria just at the opening of the alveolus. The tissue carrying these endings is extremely thin and is at the very beginning of the respiratory part of the lobule. Figure 2 displays the specialized nature of these receptors. Adrian (9) in 1933 accomplished the difficult technical feat of isolating four, and even one vagus afferent fiber in the cat. He was able to measure the passage of nerve impulses in these simplified trunks by determinations of changes in potential. He found that, on inflation of the lungs, impulses start from the receptors in the alveolar ducts and atria and pass to the respiratory center where they inhibit inspiration. If the lungs are kept inflated, these inhibitory impulses continue to flow to the center. If carbon dioxide accumulates sufficiently as a result of apnea or if serious oxygen lack develops, however, the center will break through and inspiration will occur in spite of the continuous inflow of inhibitory impulses.

When the lungs are deflated past their ordinary extent, a second set of impulses passes up the vagi, again from receptors practically in the alveoli, and these impulses excite inspiration. Such fibers go into action when a lung is collapsed by pneumothorax and account in part for the immediate hyperpnea which may attend such an experience. The possible utility of these fibers in resuscitation is made much of by Thompson and Birnbaum (10), who found that dogs which had ceased to breathe could be revived by blowing nitrogen into the trachea and sucking it out again so as to overdeflate the lungs. On the basis of this experience, they advocated devices for resuscitation which blew air into the nose and mouth through a tightly fitting face mask, and sucked it out on the suction stroke of the pump used for artificial respiration.

The modern conception of the respiratory center is that it is a bilateral collection of nerve cells, axones, and dendrites, constantly discharging nerve impulses to the muscles of respiration. Lacking any inflowing nerve impulses, the respiratory muscles are forced into tetanic contraction (11, 12). As respiratory inflation proceeds, more and more inhibitory impulses bombard the center, and eventually inspiration passes over into passive expiration. In addition to the main volley of inhibitory impulses arising from the lungs themselves, inhibitory impulses reach the main or medullary part of the respiratory center from the pontile part of the structure. The latter impulses seem to be of less effectiveness than those from the lungs.

It is of interest that the stimuli which stop inspiration and result in rhythmical breathing are caused by inflation of the lungs. In my opinion, this effect can be accomplished, not only by inspiratory inflation, but also by any influence which stretches the alveolar walls abruptly and tends to hold them in this position. Thus, rapidly developing pulmonary edema caused by alpha-naphthyl thiourea (antu) (13), which induces thickening and relative inflexibility of the alveolar walls, results in hyperpnea. The center continues to send impulses to the respiratory muscles and the formation of impulses in the lungs is not restrained on account of the constant size and condition of the alveoli. As a consequence, in-

creased breathing becomes inevitable. Similarly, the diffuse blocking of pulmonary capillaries by intravenous injection of starch solution checks capillary blood flow, and splints the alveoli in a fixed and expanded position. Again hyperpnea results. Walsh (14), the last observer of this reaction, noted that the hyperpnea did not occur if the vagi were divided. He used Adrian's methods for detecting afferent vagal impulses in isolated fibers, and came to the conclusion that impulses arising from receptors in small branches of the pulmonary artery might be responsible for the increased breathing. Thus, the problem is unsettled. In any event, conditions producing hyperpnea by mechanical swelling and the stretching of alveolar walls must act abruptly and continuously. When, as in cardiac failure, effects upon the lungs develop slowly and are complicated by changes in the oxygen content and hydrogen ion content of the blood, one cannot expect the abrupt onset of hyperpnea seen in such experiments as have been cited.

What has been described is essentially the Hering-Breuer reflex (15), very troublesome to medical students and to physicians interested in the control of breathing since the reflex was described in 1868. The respiratory center is essentially inspiratory, and is inhibited by impulses passing up the vagi as the lungs are distended. A second bilateral collection of cells in the center excites inspiration when the lungs are overdeflated.

In addition to these two sets of vagal endings, sensory fibers in the trigeminal and glossopharyngeal nerves and in the vagi are distributed to the mucous membrane of the pharynx, larynx, trachea, and bronchi. When these fibers are irritated, a large inspiration, followed by a violent contraction of the muscles of expiration, *i.e.*, a cough, is produced. It is noteworthy that the endings supplying afferent impulses resulting in cough are readily affected by anesthetics, while those concerned with the maintenance of breathing are resistant to anesthesia and to respiratory depressants. Also, it is important to realize that the normal nervous effects on breathing are due to changes in alveolar size. Irritant gases, such as ammonia or chlorine, cause cough. Inert asphyxiants, like nitrogen and hydrogen, however, have no more effect on breathing than does air, until the blood begins to be poor in oxygen and rich in carbon dioxide. There is no evidence that cough is caused by secretions in the finest bronchioles, alveolar ducts, atria, and alveoli. Coughing begins when secretion has moved up out of the respiratory part of the lobule.

The question as to whether pleural endings initiate cough is often asked. It is doubtful if they do. The visceral pleura and lungs are practically insensitive to pain. The parietal pleura, innervated by the intercostal nerves, is intensely sensitive. When a patient has a pulmonary embolus and experiences an infarct which involves the visceral surface of the pleura, transudation of plasma to this surface occurs promptly, and the fibrinous coating begins at once to stick to the parietal pleura and to cause typical pleuritic pain on breathing. Cough begins later, and in the presence of the pleurisy may be exceedingly distressing. It means the movement of bloody exudate out of the infarcted area into bronchioles, and eventually into the sputum. Cough, under these circumstances, is asso-

ciated with pleural involvement, but does not arise through a reflex originating in the pleura.

I am familiar with few direct studies on cough. Chevalier Jackson (16), in a bronchoscopic report upon cough, found about what one would expect. If an irritant was applied to the bronchial mucous membrane, cough occurred. If the excitant was not moved nor the intensity of stimulation increased, the expiratory reflex, *i.e.*, the cough, slowly ceased.

When it is understood that the respiratory center is automatically active in the constant discharge of impulses leading to inspiration, and that the cause of this automaticity resides in the metabolism of the cells that comprise the center, the physiological situation which results is not surprising. Nerve impulses from many parts of the body affect the breathing rate and depth, but they do not initiate inspiration. In this connection, it has been found that hard muscular exercise induces a degree of breathing far greater than can be attained by inhalation of carbon dioxide or any respiratory stimulant (17). This type of stimulus for respiration apparently arises from receptors in the muscles and is quite independent of carbon dioxide production, oxygen lack, hydrogen ion concentration, or any of the conventional causes of hyperpnea.

#### THE SYMPATHETIC NERVES

It is taken without question that, where parasympathetic fibers, such as the vagal and sympathetic fibers, innervate the same smooth muscle, they will act oppositely. So far as the lungs are concerned, this principle is confused. One would expect to counteract abnormal bronchiolar constriction, presumably produced through the vagi, by injections of adrenin or any of the drugs which stimulate the sympathetic nervous system. Every one knows that within reasonable limits this is true. In order to illustrate the confusion now controlling our ideas of the finer reactions within the lungs, however, I must point out that stimulation of the sympathetic components of the posterior pulmonary plexus causes an appreciable degree of bronchoconstriction, just as results through stimulation of the vagi. No doubt the complicated and extensive relations in this plexus account for some of the contradiction which exists. The facts seem to be that adrenin, ephedrine, and sympathetic mimetic drugs act upon the neuromuscular motor endings in the lungs, just as they do elsewhere. Consequently, one may rely upon injections of adrenin to relax bronchoconstriction in an asthmatic attack.

#### THE BLOOD FLOW THROUGH THE LUNGS

As the functions of the pulmonary alveoli are to deliver oxygen to the blood and to remove carbon dioxide from it, the control of the pulmonary circulation is a major factor in respiration. The lung capillaries are arranged as a net about the alveoli through which the blood flows in a sheet. The individual capillaries are exceedingly short and sufficiently wide for two corpuscles to move through abreast. There are no long independent vessels. The arrangement is beauti-

fully adapted to receive all the blood that is thrown into it by the right ventricle and, no matter what course a red cell takes through the net, the opportunity for gas exchange is the same. The capillary surface area available in the lungs is huge, about 140 sq. M. The alveolar area for gas exchange is smaller, 90 sq. M., and the total number of alveoli in man is estimated to be about 750,000,000. At rest, about one-twentieth of their surface is used.

These data, coupled with the extreme elasticity of the lungs, lead us away from conceptions of the circulatory regulation which operates upon the systemic side. The left ventricle is a powerful muscular pump, and it drives blood into a circulation which is essentially a system of shunts. Thus, if we exercise vigorously, the arterioles and capillaries in our legs dilate and vessels which have been completely closed open to conduct blood. At the same time, similar vessels in the abdomen become constricted, thereby providing a suitable volume of blood to take care of the active regions. Such adjustments of the circulation are under the control of the vasomotor fibers of the sympathetic system. There is also in the capillaries and smallest arterioles provision for adaptive change in caliber independent of vasomotor regulation. This type of vascular change permits local increase in blood supply when the tissue involved is active. Thus, Krogh (18) showed that resting abdominal muscle in the guinea pig contained 70 to 92 capillaries per sq. mm. which were open and carrying blood. The diaphragm, contracting normally at the time of the death of the animal, had up to 2,700 open capillaries per sq. mm. Richards and Schmidt (19) showed that the number of patent glomeruli in the kidneys of frogs varied from time to time, and that the open capillaries in a single glomerulus might increase in number during active diuresis.

Therefore, whenever the activities of a tissue require more blood, not only is a freer supply shunted to it by vasomotor adjustments, but the vessels in the tissue involved undergo a receptive dilatation. Capillaries, hitherto closed, open, so that a maximum working efficiency is assured. This statement has not been proved for all tissues, but is a fairly safe generalization.

Similarly, if a region in the skin is touched with a hot needle, pricked with a pin, or if for any reason a minute focus of infection begins to develop, all of the capillaries in the region involved become open for blood flow, and individual vessels dilate to an obvious degree.

In each of these examples, a part of the systemic circulation has required more blood. The vessels cooperate in providing blood quite outside the reactions of the vasomotor system. There are undoubtedly many causes of vasodilatation. There are sympathetic vasodilator nerves, and acid metabolites cause relaxation of arterioles and capillaries. The best explanation, however, of the sharply defined dilatation seen in inflammation and in circumscribed local activity is the axone reflex. In essentials, this reflex does not involve the spinal cord. It depends upon the existence of pain receptors, *e.g.*, in the bronchial mucous membrane, in which originate impulses that travel towards the cord and are interpreted as pain. The axones carrying these impulses branch and twigs carrying

impulses are supplied to the nearby arterioles and capillaries, which consequently dilate.

There is no doubt in my mind that axone reflexes account for inflammatory reactions in the nasopharynx, larynx, trachea, and large bronchi. These regions are supplied by the systemic circulation and they are highly sensitive to pain. There is no doubt that the painful onset of a trachitis or bronchitis, with swelling of the mucous membrane and transudation of watery fluid, is highly typical of axone reflex causation.

The explanation of these useful changes in blood supply is still a matter for controversy. Thomas Lewis (20) believed that exercise, heat, cold, pain, irritation of any sort, caused the elaboration in the tissues of an H substance, which acted directly on the capillaries. A little later the discovery and exploitation of histamine provided a compound ideally ordered to act upon blood capillaries so as to produce the changes we call inflammation. Histamine proved to be a compound readily formed in most parts of the body. It was rapidly destroyed, but, while present, dilated blood capillaries and made them much more permeable. It also contracted arterioles, but this action varied in different animals. Best, Dale, Dudley, and Thorpe (21) recovered histamine in large quantities from the lungs, particularly of guinea pigs. In these animals, the constrictor effect of histamine on the bronchioles can readily be great enough to kill if even a very small intravenous injection is given. As histamine acts upon systemic arterioles and capillaries, it is reasonable to expect that it would affect the vessels of the bronchial mucous membrane, which are systemic in origin. The previously mentioned axone reflex mechanism in inflammation of the bronchi and bronchioles is a mechanism in which histamine has a part.

No one can say in what tissues of the lungs histamine arises, but certainly the commanding effects of the compound are exerted upon the bronchioles. As one of the effects of histamine is to increase capillary permeability, one might expect it to be a prime cause of pulmonary edema. Another circulation is involved in pulmonary edema, however, and the respiratory pulmonary capillaries are quite separate from the systemic supply to the bronchioles. On stimulation of the vagal and sympathetic nerves to the lungs, effects upon the bronchi are readily elicited, but this is not true of the pulmonary circulation. Adrenin injections and sympathetic stimulation may be shown to cause a trifling degree of constriction of the true lung vessels. The effects are very insignificant, however, and one is left with the impression that the circulatory bed of the lungs is large enough to take care of all the blood supplied by the right ventricle. Moreover, the diffuse net of capillaries which surrounds each alveolus is so extensive and so evenly placed that it makes no difference which branches in the net are conducting blood.

If the lung capillaries possess independent capacity to close and open, we should expect histamine to affect the pulmonary circulation to a marked degree. This has not been shown to be the case, unless at the same time constriction of the bronchi occurs (22). The most that can be said of the effects of histamine on the

pulmonary circulation is that it has a slight constrictor effect on the pulmonary arterioles. This action is enough to cause a trifling rise in pulmonary blood pressure, but the more important effects, capillary dilatation and increased capillary permeability, have not been shown to take place. Efforts have been made (23) to show that the lung capillaries have independent powers of contraction and relaxation similar to the systemic vessels. Such experiments have required direct visualization of the alveolar capillaries in mammals. Thus far, the results have not been convincing for there is no assurance that the output of blood from the right ventricle remained unchanged when the pulmonary vessels under observation conducted or failed to conduct blood.

The issues involved are not academic in the least. It should be emphasized that, in the final analysis of the pulmonary circulation, there is as yet no reason to believe that the pulmonary capillaries behave like those in the systemic circulation. Thus, it cannot be said with certainty that inflammation, as it progresses in areas of the lungs serviced by the pulmonary circulation, behaves in the same way as inflammation in regions of the systemic circuit. In the bronchi and bronchioles, where the circulation is systemic, expectations of a characteristic active hyperemia will be realized, as in the skin and other regions. In contrast, the course of physiological events following injury or irritation to an alveolus is still unknown. It is not established whether the respiratory circulation to the area is shut off, becomes more active, or is unaffected until progress of the injury causes actual harm to the tissue.

The active hyperemic reaction of inflammation is one of our oldest physiological experiences. I believe that this reaction is quite as normal as the secretion of gastric juice, but, because the hyperemia reaction so often goes with destructive phenomena, it is relegated to the mercies of the pathologists. We need to know the first physiological reactions which occur when an irritant invades an alveolus. At the present time our knowledge does not provide such information.

There is a final point in regard to independent adaptive changes in the lung capillaries. Whenever such changes occur in the systemic circulation, their purpose is to provide the area in question with more arterial blood. The lungs, however, are the arterializers. They furnish the blood with oxygen just as effectively as the right ventricle is filled with venous blood and pumps it through the lung capillaries. There is no question of greater need for blood in one section of normal lung over another. It is only when alveoli are subject to infection or irritation that one may think an increased supply of blood would be advantageous. As mentioned previously, however, there is no evidence that the pulmonary capillaries and arterioles display the characteristic features of inflammation seen in the systemic vessels. It is to the vessels in the bronchial walls and in the larger pulmonary blood vessels that one must look for the usual findings of reactive hyperemia.

Where the capillaries from the bronchial artery join the true pulmonary capillaries, *i.e.*, at the beginning of the respiratory part of the lobule, there is a vascular region which is peculiar in that the systemic bronchial vessels connect suddenly with a vastly greater capillary bed than their own size and number warrants. It

is probable that at the point of anastomosis the bronchial circulation slows to a considerable degree. Miller (4) suggests that such a slowing of the circulation might be the reason that this transitional circulatory zone is a favorite site for the development of tubercles in both experimental and human infections.

#### THE THORACIC WALL

The nerves underlying the thoracic pleura arise mainly from the intercostals and are characterized by their great sensitivity to pain. They take no part in the normal physiology of breathing, but become an extreme source of distress in pleurisy and particularly in carcinoma, when the apex of the lung is involved. In this latter case, section of the posterior roots of the nerves concerned may become necessary. The usual pain of pleurisy is experienced during breathing. The region involved is moved as little as possible by the patient, but I know of no reflex cause for reducing the motion of an affected side of the chest. The patient, by remaining very quiet, reduces his total ventilation as much as possible. Movement of the inflamed region is further restricted by lying upon it or by strapping.

#### GENERAL CONSIDERATIONS

In the preceding material, an attempt has been made to describe the nerves and the functions of the nerves in the lungs and thoracic wall. This descriptive effort may be summarized as follows:

1. The motor, or efferent, nerves to the lungs are vagal and bring about bronchoconstriction when stimulated.

2. There is evidence, which is never very striking, that vasomotor nerves reach the pulmonary arteries and cause both constriction and dilatation. In no case are these effects marked and the lack of vasomotor innervation of the lung vessels does not mean functional inadequacy. The pulmonary circulation is apparently organized to accept the output of the right ventricle, whatever it may be, rather than to achieve delicate adjustments of blood flow such as localized necessity for oxygen may demand.

3. The major inherent innervation of the lungs is afferent and is concerned with the maintenance and adequacy of rhythmical breathing. Vagal receptor endings are found at the beginning of the alveolar ducts and atria. Impulses from these nerves inhibit inspiration, and expiration follows. There are other receptors in the same biological areas which induce inspiration if the alveolar ducts and atria have been overcollapsed.

4. Powerful expiratory effects—cough—are the result of sensory endings in the bronchial mucous membrane, and these receptors become fewer and fewer as the smallest bronchioles are reached. These endings are readily fatigued and anesthetized. In patients they are more evident and troublesome if the stimulating foreign body in the bronchus is movable and so contacts fresh sensory endings.

5. The lungs themselves are very insensitive to pain, but the parietal pleura



is highly sensitive, and it is from this region that pain in pulmonary disease is usually derived.

These seem to me to be the main functional effects of the lung nerves, *i.e.*, the nerves arising in or acting within the lungs themselves. It would be unfair to the development of our knowledge, however, if I failed to discuss certain relations of the breathing mechanism with outside influences, relations which even a few years ago were not suspected and which may have place in the pathogenesis of lung disease.

First of all, it is well known that pain stimulates breathing. There does not seem to be anything specific about this phenomenon. A heavy inflow of pain stimuli alerts the entire receptive sensory apparatus, and it is not surprising to find that the respiratory center reacts more readily than in normal quiet conditions.

Added to the simple matter of pain are much more definite reflex effects. These correlate events in the circulatory and respiratory systems most advantageously for the individual. It is strange that so many years had to pass before the interdependence of breathing and circulation was realized and a mechanism for correlation of the two systems discovered. About twenty years ago, it was found that accessions of pressure, particularly if experienced suddenly in the arch of the aorta and in the carotid artery just before it enters the skull, caused reduction, or even cessation, of breathing. The nerve endings or pressure receptors, through which these alterations in breathing are mediated, were found to transmit impulses to the respiratory center by the depressor nerves from the aortic arch, or by nerves from the region of the division of the carotid arteries, the carotid sinuses.

The effects of the pressure receptors on breathing were, however, soon overshadowed by those discovered to be due to chemoreceptors in the same regions. As time passed, it became clear that in the aortic arch and in the carotid sinuses there were nerve endings which, on rise of blood pressure, caused diminution of breathing and reduction of blood pressure. These effects were mediated through the respiratory and vasomotor centers. Similarly, if blood pressure fell abruptly, the influence of these pressure receptors was to increase breathing and blood pressure. These effects were not, however, so important as were those found to depend upon nerve endings in the same region, which responded to chemical stimuli, particularly oxygen lack.

The nerves from these outlying regions which affect breathing are not in the lungs and so are outside my subject. The actions of these nerves have been examined so extensively and with such enthusiasm that the aortic arch and carotid sinuses have come to be regarded virtually as accessory respiratory centers. It is only natural that, in the interpretation of both clinical and experimental observations, an attempt should be made to ascribe effects upon lung capillaries and bronchioles to reactions originating in these new foci which enter the regulation of breathing and blood pressure so potently. Naturally, the issues which have come under discussion are not those of lung infection, but are concerned with the development of lung edema, particularly lung edema which comes suddenly.

Recently, for example, Luisada and Sarnoff (24) have given huge intra-arterial injections of salt solution to anesthetized dogs. When the infusions were via the carotid artery, so that the carotid sinus was immediately involved, pulmonary edema resulted. In contrast, when similar volumes of salt solution were given intravenously, pulmonary edema rarely occurred. These investigators believe that the permeability of the lung capillaries is under nervous control and can be affected through the carotid sinus. The idea is interesting, but, as it requires postulating a novel control of the pulmonary circulation, it must be subjected to much hard thought and exacting experiment.

It is far outside my subject to go further with these effects of nerves on the lungs which are mediated from various remote parts of the body. I have attempted to present the direction in which physiological research upon the lungs progresses. The complexity and delicacy of the lung tissue have made direct experiments difficult and unconvincing. Nevertheless, the great advances in anesthesia, in knowledge of breathing, and in the adroit surgical manipulation of lung tissue, make me feel confident that within a decade we shall progress rapidly and that many of the mysteries which beset you as clinicians, and to which I have referred, will be lost in the pile of conquered medical problems.

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# THORACOPLASTY AND PULMONARY RESECTION IN THE TREATMENT OF TUBERCULOUS TRACHEOBRONCHITIS<sup>1,2</sup>

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## INTRODUCTION

The purpose of this report is to present the results obtained in the treatment of tuberculous tracheobronchitis by thoracoplasty and pulmonary resection. It is evident from reviewing the literature that pneumothorax, phrenicotomy, and the local treatment of these lesions have failed to control the disease or prevent its complications and sequelae. Indeed, numerous investigators have demonstrated that the marked reduction in pulmonary function and the complications resulting from these procedures are often more serious and difficult to deal with than the original lesion.

Phrenicotomy in the treatment of tuberculous tracheobronchitis is now condemned because it deprives the diaphragm of its expulsive power and aids in the retention of pulmonary secretions which are the prime factors in the development of atelectasis.

The local application of the cautery, either chemical or electrical, through a bronchoscope, has been disappointing. Usually the bronchial lesion is so extensive that complete visualization is impossible and hence treatment is seriously handicapped. In bronchial stenosis, mechanical dilatation, combined with the cautery, will effect a temporary improvement, but, as healing is by fibrosis, recurrence of the stenosis is inevitable. Such procedures cannot restore the normal anatomical and physiological pattern, as the mucosal, muscular, and cartilaginous layers have been destroyed and replaced by fibrous tissue. Cauterization may be indicated in the small circumscribed ulcers which do not involve the circumference of the bronchial wall.

During the past six years Tuttle (1), Brantigan (2), Chamberlain (3), Rafferty (4), Davies (5), and others have reported on the value of artificial pneumothorax in the treatment of tuberculous bronchitis. Some of these writers conclude pneumothorax is of value only in minimal lesions. Others believe pneumothorax will control 30 to 40 per cent of the cases. They all recognize the hazards associated with artificial pneumothorax, and the high incidence of atelectasis, pleural effusion, empyema, and bronchopleural fistula. Many of the arrested cases have the sword of Damocles over them, for it is difficult to determine when one of the above complications will develop. Unfortunately, the occurrence of such complications often results in a non-functioning, inexpandable lung. In view of the questionable results with the above procedures, the present writers have elected to employ thoracoplasty or pulmonary resection in 83 cases of definitely proved tuberculous tracheobronchitis.

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<sup>2</sup> Presented before Mississippi Valley Trudeau Society, September 7, 1947.

## CASE SELECTION

The thoracoplasty cases were selected on the basis of bronchoscopic visualization of deep-seated tuberculous inflammation with accompanying excessive bleeding on slight provocation, the presence of ulceration or tuberculoma, or the finding of bronchial stenosis. The lesions were classified as acute or chronic, depending upon the degree of clinical toxicity associated with their presence.

The indications for pulmonary resection were similar to the above, but, in addition, several cases have been included which, although not presenting bronchoscopic evidence of bronchitis, did show extensive involvement of the bronchial wall after the lung was resected.

## RESULTS

Eighty-three patients were subjected to 53 thoracoplasties and 50 pulmonary resections. Twenty-two had a primary thoracoplasty followed by a pulmonary resection. As noted in other studies, there was a higher incidence of tracheo-

TABLE 1

*Results from thoracoplastics*

	ARRESTED	CLINICALLY IMPROVED BUT INTERMITTENTLY POSITIVE FOR TUBERCLE BACILLI	NO IMPROVE- MENT OR WORSE	DIED	TOTAL
Acute.....	12	9	3	2	26
Chronic.....	13	13	0	1	27
Total.....	25	22	3	3	53
Per cent of total....	48 per cent	41 per cent	5½ per cent	5½ per cent	100 per cent

bronchial disease among the women (56) as compared to the men (27). Each bronchus appeared about equally vulnerable as involvement was observed 43 times on the right side and 40 times on the left side.

*Thoracoplasty:* Fifty-three patients received from 3 to 6 stages of thoracoplasty. Sputum conversion occurred in 25, or 48 per cent of these patients, and they were discharged from the sanatoriums as arrested. Twenty-two or 41 per cent had marked clinical improvement with considerable reduction or absence of sputum and the disappearance of the evidences of toxicity. In every one of these, however, the sputum and gastric washings were intermittently positive for tubercle bacilli either by smear or culture. All of these patients had pulmonary resection at a later date. In the remaining 6 cases, 3 showed no improvement or became worse, and 3 died. Approximately one-half (26) were toxic and acutely ill. The results are tabulated in table 1.

*Pulmonary Resection:* Pulmonary resection was carried out in 50 patients with but one fatality. However, only 40 patients have been observed for a period of four or more months. Therefore, the following statistics and discussion will

include only the latter group. One patient, who died the third day postoperatively, is not included in the follow-up statistics.

In the follow-up studies the sanatorium physicians were requested to report their opinion as to the prognosis of the patients. They stated the results were excellent in 19, good in 8, fair in 6, and poor in 6. Their impressions, however, refer to the general condition and probable ability of the patient to rehabilitate himself, and not to the control of the bronchitis and conversion of the sputum. The status of the last-named features is demonstrated by the fact that cultures of the gastric washings of 32 patients revealed no tubercle bacilli, while these

TABLE 2  
*Results as related to predominant lesions*

TYPE OF LESION	ARRESTED	CLINICALLY IMPROVED BUT INTERMITTENTLY POSITIVE	TOTAL
Acute bronchitis.....	4	2	6
Chronic bronchitis.....	7	3	10
Bronchial stenosis.....	10	1	11
Bronchiectasis.....	11	1	12
Total.....	32	7	39

TABLE 3  
*The effect of operative procedures on end results*

TYPE OF OPERATIVE PROCEDURE	ARRESTED	CLINICALLY IMPROVED BUT INTERMITTENTLY POSITIVE	TOTAL
Primary resection.....	13	2	15
Resection secondary to thoracoplasty.....	19	5	24
Lobectomy.....	13	2	15
Pneumonectomy.....	19	5	24

organisms could be demonstrated in the gastric washings or sputa of only 7 patients.

In table 2 it may be seen that lobectomy or pneumonectomy offers approximately the same prognosis in acute or chronic bronchitis. Better results can be anticipated in bronchial stenosis or bronchiectasis. All acute lesions received streptomycin preoperatively until the bronchi appeared quiescent.

Statistically, primary resection seemed to fare better than resection secondary to thoracoplasty. However, primary resections for the most part were performed recently and had the benefit, when indicated, of both streptomycin and penicillin. Lobectomy was the procedure of choice in 15 patients and pneumonectomy in 24 (table 3).

Chemotherapy as an adjunct to pulmonary resection has been of considerable

value, as shown by a smooth postoperative course, a minimum of postoperative complications, and what appears, at least at present, as an excellent clinical end result. Streptomycin combined with penicillin seemed most efficacious, although penicillin combined with sulfadiazine was a great aid (table 4).

The preoperative respiratory function was classified as good in 18, fair in 17, and poor in 4 patients. The latter group had extensive bilateral tuberculosis with bronchitis limited to one side. The estimations of functional capacity were made from clinical evaluation.

The complications encountered in this series may be seen in table 5.

TABLE 4  
*Effect of chemotherapy*

DRUG	ARRESTED	CLINICALLY IMPROVED BUT INTERMITTENTLY POSITIVE	TOTAL
Streptomycin and penicillin.....	6	0	6
Penicillin and sulfadiazine.....	23	4	27
Sulfadiazine or no chemotherapy.....	3	3	6
Total.....	32	7	39

TABLE 5  
*Postoperative complications*

Bronchopleural fistula with tuberculous empyema.....	1
Tuberculous empyema—at present a small sinus tract.....	1
Reactivation in another lobe or contralateral side.....	2
Expectoration of silk suture.....	1
Contralateral pleural effusion.....	1
Emotionally unstable following surgery.....	1
Total.....	7

## DISCUSSION

Heretofore, the outlook of individuals afflicted with tuberculous tracheo-bronchitis was most discouraging, both as to mortality and morbidity. In several studies, depending upon the method of case selection, the case mortality rate has ranged from 40 to 85 per cent. Samson (6) clearly showed that a fatality rate of 50 per cent can be expected within two to four years. In addition, those surviving can anticipate an unhappy and miserable existence, with an uncontrollable cough and the raising of copious amounts of purulent sputum. Streptomycin therapy may alter the course of tuberculous tracheobronchitis, but it is still too early for any conclusive statement on the subject.

In the treatment of tuberculous tracheobronchitis, the physician is faced with the practical problem that the persistent bronchitis is situated in the path of pulmonary secretion coming from an active parenchymal lesion. The control of the parenchymal lesion would appear as the crux or keystone to therapy.

In the presence of constant irritation by coughing and purulent secretions, there is little opportunity for any lesion to heal. Nature heals wounds more easily in the absence of pus and with the diseased part at rest.

The procedures employed in the past either failed to control the parenchymal disease or often produced bronchial obstruction, which led to atelectasis with secondary suppurative pneumonitis, cavitation, extension of disease, and tuberculous empyema. In the present series, only one major and several minimal atelectases occurred. This low incidence of major atelectasis can be attributed to an alert and prepared resident staff always aware of minimal pulmonary changes. In thoracoplasty, the collapse is initiated peripherally and proceeds towards the hilum. In pneumothorax, the collapse is concentric, affecting the major bronchi as well as the parenchyma.

It is believed that this small series definitely demonstrates the superiority of thoracoplasty and pulmonary resection over the previously mentioned methods. Sputum conversion occurred in 46 per cent of the patients with thoracoplasties and 86 per cent of the group with resections. Two patients, who continue to discharge tubercle bacilli and in whom bronchoscopy revealed persistent bronchitis, are now receiving a trial of streptomycin. A third patient may attain sputum conversion when all of her secondarily infected bronchial silk sutures are expectorated.

The operation of choice for tuberculous bronchitis has varied between thoracoplasty and resection. Until recently it was considered advisable to perform a preliminary thoracoplasty before undertaking lobectomy or pneumonectomy. The reasons for this practice were: (1) toxicity and the quantity of sputum could be reduced in "wet" and desperate risk cases; (2) overdistention of the remaining lobes could be prevented; (3) an acute bronchitis could be converted into a chronic one; and (4) a large percentage of lesions could be controlled by thoracoplasty. Primary resection was limited to bronchial stenosis associated with recurrent suppurative pneumonitis. The use of streptomycin and penicillin has considerably altered the situation. Chemotherapy, when combined with postural drainage preoperatively and phrenicotomy or partial thoracoplasty following resection, will now control toxicity, excessive secretions, acute bronchitis, and overdistention of the remaining lobes. Consequently, at the present time the writers favor primary pulmonary resection for tuberculous bronchitis and reserve thoracoplasty for unilateral lesions associated with minimal parenchymal disease, and for acute bronchitis which fails to respond to streptomycin.

Unfortunately, in the selection of cases, enthusiasm for a new method of treatment is occasionally misleading. For example, thoracoplasty was undertaken in 3 desperate risk cases with bilateral active disease with bronchitis limited to one side, in the hope of stemming a progressively downward clinical course. All 3 patients died. In another 2 patients with extensive pulmonary involvement, resection produced respiratory cripples. One of these was a respiratory invalid before surgery which was performed to control suppurative pneumonitis. The second patient has had a marked decrease in respiratory reserve due to the contralateral pleural effusion. It should also be kept in mind that reactivation



of an old lesion is always possible months and years after a lobectomy or pneumonectomy. Such reactivations, however, should not be regarded as "spreads." An attempt should be made to prevent reactivation by reducing to a minimum the possible distention of remaining lobes or contralateral lung. This may be accomplished by a phrenicotomy or a five- or six-rib thoracoplasty either at the time of surgery or shortly thereafter.

The recent literature has provided considerable space to the problem of contralateral "spread" in pulmonary resection for tuberculosis. There was but one "spread" to the contralateral side in the present series. This occurred in a case early in the series when a bronchopleural fistula and tuberculous empyema developed, with spilling of the purulent secretions to the contralateral side. The prevention of "spread" was probably due to: (1) preoperative reduction of pulmonary secretions to a minimum; (2) conversion of acute bronchial lesions to a chronic state; and (3) prevention of spilling of secretions to other lobes at the time of surgery.

At present all acute cases are placed on streptomycin (1.0 gram daily) and penicillin 300,000 units in eight to ten divided doses daily. Postural drainage is performed preoperatively six times per day in "wet" cases until the sputum output reaches a low plateau. During surgery "wet" patients are either placed in a 20° Trendelenburg position to facilitate drainage of secretions into the trachea, or the bronchus is packed with a trimmed tampax. Last but not least, frequent aspirations of the trachea are performed by a trained anesthetist.

The use of individual ligation of the hilar structures and modern chemotherapy have indeed controlled the major complications seen in the past. Bronchopleural fistulae, tension pneumothorax, and pyogenic empyema are rarely seen today.

Thoracoplasty and pulmonary resection are not without their problems. During surgery, particularly with lobectomy or pneumonectomy, blood should be administered freely. If a tuberculous cavity is opened, 2.0 grams of streptomycin and 100,000 units of penicillin should be inserted into the pleural space. Postoperatively, streptomycin and penicillin should be given parenterally and into the pleural space when indicated. Chemotherapy has prevented serious involvement of the pleural space in 3 cases where a tuberculous cavity was inadvertently opened. Postoperatively, patients must be encouraged to breathe deeply, cough, and expectorate secretions at hourly intervals. Their position in bed is changed regularly to prevent pulmonary stagnation. If atelectasis develops, intensive effort to release the bronchial obstruction is carried out, *i.e.*, CO<sub>2</sub> inhalation, forced coughing, deep breathing, and frequent changes in position. If these measures are unsuccessful, tracheal aspiration by means of laryngoscope and catheter should be performed. Bronchoscopy is seldom necessary. Pain may be controlled by morphine in doses ranging from 0.005 to 0.010 gram, but the drug should be used with care to guard against the possibility of respiratory depression.

The low case mortality rate of 5½ per cent for thoracoplasty and 2 per cent for the pulmonary resections of the present series certainly speaks favorably for

these procedures. Many of the patients were desperate risk cases with little pulmonary reserve. The only death in the pulmonary resection series was also the only one in which mass hilar ligation was used.

#### CONCLUSIONS

Pulmonary resection and thoracoplasty are the operations of choice in persistent tuberculous tracheobronchitis because of: (1) the high incidence of sputum conversion; (2) the low incidence of complications; and (3) the low case mortality rate.

#### SUMARIO

##### *La Toracoplastia y la Resección Pulmonar en el Tratamiento de la Traqueobronquitis Tuberculosa*

La resección pulmonar y la toracoplastia son las operaciones de elección en la tuberculosis traqueobronquial persistente, debido a: (1) alta proporción de virajes del esputo; (2) baja proporción de complicaciones; y (3) baja mortalidad.

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# EXTRAPLEURAL PNEUMOTHORAX<sup>1,2</sup>

## A Five Year Study

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Since the description of pleurolysis (2) by Tuffier in 1891, the question of the precise value of the operation of extrapleural pneumothorax has created a division of thought among those interested in the collapse therapy of pulmonary tuberculosis. The enthusiasm in 1936 for the then recently introduced operation became tempered with caution as unfavorable results, caused by overextension of indications and improper postoperative care, plagued the pioneers of the procedure. The ultimate fate of the extrapleural space was unknown. Many abandoned the procedure completely, condemning it as unsatisfactory and too dangerous, some reserved judgment, and others continued to use the operation.

The present report consists of an evaluation of the five year results (April 1938 to May 1942), observed in a series of 45 patients who were submitted to 52 operations. Three operations, performed subsequently, are also reported because they represent contralateral surgery on patients included in the series by virtue of their first operation.

### INDICATIONS FOR OPERATION

Because the institution of a procedure in the extrapleural space demands close medical supervision and coöperation on the patient's part, the emotional and mental stability of each patient should be critically surveyed before such a venture is undertaken. The time for this study is usually afforded while other less extensive collapse measures are in progress. The importance of this factor will be reëmphasized during the analysis of results.

It is the practice of the writers to attempt intrapleural pneumothorax on all suitable patients. The failures usually fall into three groups: (1) those in which the initial attempt fails, due to pleural symphysis; (2) those in which intrapleural pneumothorax fails to control the disease because of adhesive bands which cannot be severed by closed pneumonolysis; (3) those in which intrapleural pneumothorax gives promise of effectiveness, but is eventually unsuccessful because of obliterative pleuritis.

As a rule, with predominately upper lobe lesions, group (1) is considered for thoracoplasty or extrapleural pneumothorax; group (2) for thoracoplasty, open

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pneumonolysis and extrapleural pneumothorax; and group (3) for thoracoplasty or extrapleural pneumothorax.

On a number of occasions, pneumoperitoneum has been induced to prevent further progression of the tuberculosis prior to deciding upon surgery. In a few of these instances, the diseased portion of the upper lobe has become atelectatic and has migrated to the mediastinum, where it has remained by virtue of pressure from the expanding inferior healthy pulmonary tissue. On these infrequent occasions, surgery is obviated and the pneumoperitoneum becomes the definitive procedure by the production of a "medical lobectomy."

In the main, if the lesion is more exudative than productive, the writers favor the induction of extrapleural pneumothorax; if the lesion is more productive than exudative, thoracoplasty is considered to be advisable. However, slight retraction of the mediastinal structures and roentgenographic evidence of thickened pleura are not always expressions of the current parenchymal disease, which may be exudative or readily compressible. A moderate thickening of the pleura, as detected by roentgenogram, is often deceptive and is not considered a contraindication because at operation the extrapleural plane may be ascertained and developed with relative ease.

Cavernous pulmonary tuberculosis constitutes a contraindication when the cavity is large and peripherally located, so that the pleura represents one of its circumferential borders. Some phthisiologists (5) have not been deterred by this factor, but the fear of bronchial fistulae has made the writers reluctant to apply extrapleural stripping to this type of lesion.

The procedure has not been applied to the so called "tension cavity". Nevertheless, Reid (11) states "Tension cavities react better to this form of treatment (extrapleural pneumothorax) than to thoracoplasty, unless there is bronchial stenosis, because concentric relaxation allows reopening of the draining bronchus, and the actual positive pressure of air in the extrapleural pneumothorax space compresses the cavity."

Pulmonary lesions, complicated by acute ulcerative tracheobronchial disease, constitute a definite contraindication to the extrapleural type of collapse.

The value of the operation in selected bilateral lesions is unquestioned. Combinations of thoracoplasty-extrapleural pneumothorax, bilateral extrapleural pneumothorax and intrapleural-extrapleural pneumothorax, may be successfully employed.

It must be appreciated that the indications for extrapleural are not sharply defined. In some instances, the decision is not an easy one, and, as the more intelligent patient soon becomes conversant with collapse measures, his wishes may be consulted before a final choice of operation is made. In the present series, it was the usual practice to explain to the patient that, should extrapleural pneumothorax prove not technically feasible, it would be converted to a first-stage thoracoplasty at the time of operation.

Although the operation was not used in this series as a preparatory device for a later thoracoplasty, it is comforting to realize that thoracoplastic collapse is available if extrapleural pneumothorax fails.

It should be stressed that extrapleural pneumothorax is not advocated as a substitute for thoracoplasty, but rather that, in selected cases, the indications for thoracoplasty can be narrowed in favor of extrapleural pneumothorax.

#### OPERATIVE TECHNIQUE<sup>6</sup>

In the preoperative preparation, measures are instituted that are consistent with a major surgical procedure. The patient is encouraged to cough and expectorate before coming to the operating room. Inhalation anesthesia is employed, either cyclopropane or gas-oxygen-ether mixtures. The patient is placed in the lateral recumbent position with the upper arm drawn well forward.

A slightly curved incision, with the convexity inferiorly, is made over the fourth intercostal space from the edge of the erector spinae muscle to the inferior angle of the forward drawn scapula. The incision can be lengthened to accommodate a first-stage thoracoplasty, if extrapleural separation does not prove feasible. The trapezius and rhomboid muscles are divided in the direction of the incision. A pedicled flap of extracostal fascia, including the insertion of the serratus posterior superior muscle, is developed. The flap begins at the inferior margin of the fifth rib and extends to the superior margin of the third rib. The width of the flap is slightly greater than the length of the fourth rib to be resected. The erector spinae muscle is carefully stripped so it can be preserved as a medial flap. The last two steps are important for proper closure. Approximately 10 centimeters of the fourth rib, extending laterally from the transverse process, are resected subperiosteally.

As the deep periosteal bed is incised, there is often exposed a group of muscle fibers which represent expansions from the internal intercostal muscles (10). Division of these muscle fibers exposes a grayish-white membranous layer. This lamina, in well nourished individuals, contains small particles of fat and represents the areolar tissue between the parietal pleura and deep periosteal layer.

A finger is then inserted in the chosen stratum and the stripping is commenced and continued until the limits of the finger are reached. Further dissection progresses, using a lighted retractor, with a small bit of gauze clamped in the end of a long curved hemostat. Pressure is directed toward the thoracic wall rather than against the lung. The parietal pleura can be seen as a tight fold which always lags behind the lung.

If resistant adhesions are met in one direction, the area is temporarily abandoned and the recalcitrant adhesions approached from another angle. This maneuver will often forestall sharp dissection. Apical adhesions or sites of an old pleuritis will occasionally defy blunt dissection and must be incised.

The dissection is considered adequate when the seventh rib posteriorly, the fifth rib laterally, the third rib anteriorly, and the exposure of the vena azygos on the right and the mid-aortic arch on the left, are reached. This constitutes a circumferential collapse of the apex, carried to the hilum of the lung, with the edges curved slightly downward and giving the appearance of a flattened dome. Even when the roentgen study indicates that a lesser collapse may control the lesion, the described limits are employed. It is easier to reexpand the lung than to attempt additional collapse by air pressure, and after a few days have elapsed it may be extremely difficult to increase the size of the space by the use of increased extrapleural pressure (figure 4). In a few cases the anterior, lateral, and posterior dissection has been greater because of more extensive disease.

<sup>6</sup> The majority of operations were done by one of us (P. C. S.) and the remainder either by H. Brodie Stephens, M.D., or by Glenroy N. Pierce, M.D., of San Francisco.

Bleeding is controlled by gauze packing, ligature and electrocautery. If the latter is necessary, the anesthesia is changed to nitrous oxide. A hot moist gauze pack is placed in the space for ten minutes while the periosteal flaps and closing preparations are in progress.

In closing, airtightness is mandatory. To be successful, the first two layers of the routine six-layer closure must be without leaks. The posterior periosteum of the rib above and below is divided longitudinally in its mid-portion, slightly longer than the length of the rib resection. This step is relaxing in nature and facilitates the subsequent closure of the periosteal bed of the fourth rib. An alternate procedure is to incise partially the intercostal muscles longitudinally. The intercostal nerve is crushed and the intercostal vessels sutured mesially. The first layer closure is composed of posterior periosteum and intercostal muscles, reinforced medially by the erector spinae muscle. The second layer is the previously prepared pedicled fascial flap, which is imbricated over the first stratum. The third and fourth layers represent closure of the rhomboid and trapezius muscles, the fifth consists of the subcutaneous tissue and the sixth, the skin. Fine interrupted silk sutures are used throughout.

The practice of leaving sterile saline in the extrapleural space was discontinued early in the series, as no beneficial effect was noted.

After the wound is bandaged, the patient is turned over on his back and an 18 gauge needle inserted through the second anterior intercostal space in the midclavicular line. A pressure reading is taken with adjustment of the extrapleural pressure to atmospheric or slightly positive, usually plus twelve minus twelve centimeters of water.

#### IMMEDIATE OPERATIVE COMPLICATIONS

Hemorrhage has presented a problem in only a few instances. With thorough terminal inspection of the extrapleural space and gentle dissection, this complication should remain at a minimum. Operative exposure, although small, is sufficient to control the usually encountered arterial and venous bleeding. However, the resection of an additional rib may be necessary to cope with a serious hemorrhage.

Pleural tear, with entrance into the intrapleural cavity, results in a combined intrapleural-extrapleural pneumothorax of a greater or lesser degree. The collapse of the lower lung depends on the extent of the pleural adhesion and, if the intrapleural space is free, a total combined intra-extrapleural pneumothorax may be realized and used effectively.

#### POSTOPERATIVE CARE AND SUBSEQUENT MANAGEMENT OF THE EXTRAPLEURAL SPACE

On the morning of the first postoperative day, the patient is fluoroscoped, or a portable bedside roentgenogram is taken. Almost invariably fluid has accumulated and requires aspiration with air replacement. The lateral recumbent position is used and the needle is inserted in the most dependent portion of the space with great care to avoid inoculation of the surrounding tissues with aspirated material. Irrigation with sterile normal saline is commenced on the first postoperative day to combat blood clot formation in the extrapleural space. To ignore this principle may lead to a fixation of the lung with a greater collapse than is desirable. Following aspiration and irrigation, sulfadiazine or penicillin may be left in the space as a prophylactic measure against the development of nontuberculous extrapleural empyema.



FIG. 1A. (Upper left) Case 29. Exudative lesion right anterior 2nd intercostal space.

FIG. 1B. (Upper center) Case 29. Nontuberculous extrapleural empyema three months postoperatively. (Note extreme compression of lung beneath purulent fluid level.)

FIG. 1C. (Upper right) Case 29. Present status of reexpanded lung with linear fibrosis at site of old lesion and obliteration of extrapleural space.

FIG. 2A. (Lower left) Case 41. Right upper lobe lesion with several small cavities.

FIG. 2B. (Lower right) Case 41. Present status with right extrapleural oleothorax (See text).



FIG. 3A. (Upper left) Case 36. Bilateral upper lobar disease with cavitation.

FIG. 3B. (Upper right) Case 36. Present status with right extrapleural space obliterated and left extrapleural oleothorax.

FIG. 4. (Lower) Bilateral failure of extrapleural pneumothorax due to inadequate mediastinal dissection; these spaces could not be enlarged by increasing the extrapleural air pressure. Note sub-extrapleural cavities and infiltration of pulmonary tissue adherent to mediastinum.



Special alertness is necessary when contralateral collapse is present because the postoperative fluid accumulation may continue the extrapleural dissection and literally submerge the lung to the point of a dangerously decreased vital capacity.

Aspiration, irrigation, and air replacement are repeated at intervals of forty-eight hours, or as otherwise indicated, until the fluid balance becomes stabilized. Usually this occurs between the fifth and tenth postoperative days.

On the seventh to fourteenth day, the patient is transferred back to the sanatorium where the desired collapse is maintained by suitable fills with air at first semiweekly, then weekly, as the space becomes stabilized. The volume of air used varies and the air pressure is more constant with final readings of from 26 to 34 cm. of water positive pressure.

If the space is not dry by the fourth to eighth week, an extrapleural empyema should be suspected. These are of three types: (1) tuberculous, (2) nontuberculous, and (3) mixed. The type may be established by aspiration with bacteriological examination of the purulent fluid. The pathogenesis of the extrapleural empyema is not always clear, but presumably results from broncho-extrapleural fistulae, microscopic extrapleural tubercles, or operative or needle contamination.

The systemic reaction from extrapleural empyema is milder than from intrapleural empyema. The relatively benign character of extrapleural empyema is presumably a result of poor absorptive qualities of the membranous barrier which lines the extrapleural space. It is noted that air absorption is slower from the extrapleural than from the intrapleural space because of the diminished permeability of the artificially created lining.

Extrapleural empyema responds so well to treatment that this complication is no longer regarded with alarm. Further surgical collapse is not used to manage extrapleural empyema, except in rare instances.

The presence of a broncho-extrapleural fistula complicates the management of empyema. The fistula may be heralded by the sudden appearance of purulent sputum, by pulmonary compression beyond that expected from the volume of air fill, or by inability to attain the usual positive pressure. The presence of fistula is proved simply by the instillation of methylene blue into the space and the subsequent appearance of the dye in the sputum.

Management of a nontuberculous infection consists of aspiration, lavage with sterile normal saline, and air replacement, in order to maintain the space. One of the antibiotics, depending upon the offending bacterial flora, is left in the extrapleural space. Three or four such treatments should clear the space which has been maintained by air fills.

If the empyema is tuberculous, the extrapleural space is aspirated and lavaged as thoroughly as possible and 15 to 20 cc. of 2 per cent methylene blue in 95 per cent alcohol are instilled. This procedure is repeated every three to four days with moderate air fills until the production of purulent material is reduced to a minimum. Oil is then gradually substituted for air.

## OLEOTHORAX

The function of oleothorax is to maintain collapse and to retard the formation of purulent matter. Thus, the usual indications for extrapleural oleothorax include tuberculous extrapleural empyema and the forestalling of an obliterative process in the extrapleural space. Certain conditions should be satisfied before attempting conversion to oleothorax. The inferior limits of the extrapleural space should be firmly adherent in order to prevent further extrapleural dissection by the oil. The floor of the space should be free from fistulous communications with the bronchi and should be given time to thicken and for any soft sub-extrapleural lesions to harden. Early postoperative conversion is not advised as routine, but is sometimes done to hold a space or assist in empyema control.

Sterile mineral oil with a neutral pH and number 5 viscosity is used. The conversion is performed in multiple fills. The initial fill of approximately 30 to 50 cc. serves to test the patient's tolerance to the oil and the ability of the extrapleural space to meet the conditions described. The entire conversion extends over a period of three to six weeks with never more than 400 cc. of oil being used for any one space.

At times two layers of fluid are noted at fluoroscopy, the lower representing extrapleural fluid, which may or may not be purulent. This fluid is aspirated as indicated and replaced with slightly less volume of oil. Occasionally, the fluid disappears spontaneously and the lung expands to replace it. A small amount of fluid is not disturbed unless it is increasing or provoking symptoms.

The patients are instructed to report every three to six months for examination, or at any time that symptoms develop. It has been noted that a decrease or increase of pressure within the extrapleural oleothorax produces the same complaint, a sensation of tightness. For this complaint, the pressure of the oil is measured and readjusted, either by adding more or withdrawing the volume necessary to make the patient symptom free.

If any oil is expectorated, all of the remaining oil is immediately removed and replaced with a smaller volume of air. The extrapleural space is left with a negative pressure after each aspiration. This is especially helpful in that peripherally located fistulae may seal off between the thoracic wall and the slightly reexpanded lung. In such instances, oil may again be employed to perpetuate the collapse.

An unusual complication is extrapleural cutaneous fistula, which is managed by aspirating the oil and maintaining a negative extrapleural pressure until the lung covers the intrathoracic orifice of the fistula. Thereafter, it may be possible to proceed with the conversion to oleothorax.

In one instance in the present series, after completion of the oleothorax for a right tuberculous empyema, the lower fluid level failed to disappear after a reasonable interval. Aspiration revealed chyle, which apparently resulted from inflammatory disruption of the right lymphatic duct. This particular space was left strictly alone and no untoward effects have been observed.

The oil may be removed at the appropriate time, or it may be left indefinitely. The present tendency is to leave the oil undisturbed, unless complicating factors force its removal.

#### FATE OF THE EXTRAPLEURAL SPACE

Air fills are terminated in the same manner as those for intrapleural pneumothorax. The lung expands to its limits and the obliterative process proceeds by the formation of fluid which is eventually displaced by the fibrous thickening of the walls as they approximate and finally unite. Depending upon the size of the space, the obliteration may take from several months to several years.

#### RESULTS

Most of the patients in this series represent difficult therapeutic problems familiar to all those who practice phthisiology. The ages varied from seventeen to sixty-one years. There are 22 women and 23 men. One case was classified as minimal, and the others as moderately or far advanced pulmonary tuberculosis on admission to the sanatorium.

A total of 52 operations was performed on 45 patients. The procedure was unilateral in 39 patients, bilateral in 6 and twice on the same side in one individual. The secondary operation was performed because the lung rapidly reexpanded; the second attempt failed in like manner and the patient eventually died of tuberculosis. The operative complications which were encountered may be seen in table 1. Rupture of the parietal pleura with entrance into the intrapleural space resulted in a few combined pneumothoraces which were used effectively. There were no intrapleural empyemata.

One of the more recent cases is of interest in that a successful outcome was attained with maintenance of the extrapleural space, in spite of several complications (figure 2). In this operation, it was necessary to resect an additional rib to control hemorrhage. Subsequently, the operative wound was noted to bulge with air fills and finally ruptured, forming an extrapleural cutaneous fistula. A nontuberculous empyema followed. The fistula and empyema were managed in the usual manner and the space was filled with oil.

Contralateral "spread" was noted as early as the tenth postoperative day in one case and resulted in fatal progression. In the second case, a "spread" was discovered nine months after operation, when an intrapleural pneumothorax was established. This patient left the sanatorium against advice and later succumbed to her disease. In the third case, a "spread" was noted in the ninth postoperative month and an intrapleural pneumothorax was then successfully employed.

Ipsilateral progression resulted from the application of the extrapleural pneumothorax to a pulmonary lesion, complicated by acute ulcerative tracheobronchial disease. The circumferential collapse compressed the bronchi, producing a spread of the ulcerations, bronchial stenosis, trapped pulmonary secretions, and increased pulmonary destruction. The involved lung was reexpanded

and subjected to thoracoplasty, which afforded the necessary collapse yet interfered less with bronchial drainage.

One case presented an unusual sequence of complications. A postoperative nontuberculous empyema responded well to treatment and was then converted to oleothorax. Mineral oil soon appeared in the sputum, the extrapleural space was emptied of oil by aspiration and in a short time a tuberculous extrapleural empyema developed. The latter drained through a bronchus and was expectorated. Thoracoplastic collapse was done, but failed to obliterate the space and the empyema persisted. An Eloesser cutaneous flap drainage of the extrapleural space solved the problem. The patient is now working and the extrapleural space has been obliterated.

TABLE 1  
*Operative complications*

IMMEDIATE		LATE	
Pleural tear.....	5	Contralateral spread.....	3
Hemorrhage.....	3	Ipsilateral progression.....	1
Rapid reëxpansion.....	1	Extrapleural empyema.....	18
		Tuberculous.....	10
		Nontuberculous.....	8
		Extrapleural cutaneous fistula.....	1

TABLE 2  
*Complications of oleothorax*

Total number of extrapleural oleothoraces.....	32
Complications:	
Broncho-extrapleural fistulae.....	2
Extrapleural cutaneous fistula.....	1
Extrapleural chylothorax.....	1
Extrapleural tuberculous empyema.....	1

The eventual fate of the extrapleural space may be seen in table 3. The two spaces not obliterated represent one patient who recently had the oil aspirated from both spaces of a bilateral extrapleural oleothorax and has started the oblitative process. One of the three results listed as "unknown" occurred in a patient whose disease was reported as arrested in June 1945 by another institution. It was also reported that this patient's extrapleural pneumothorax was discontinued as effective in June 1944, but the present status of the space is not known. One of the thoracoplasties listed in table 3 was performed elsewhere for an extrapleural empyema which apparently developed after leaving the sanatorium with an extrapleural oleothorax. A report has been received that the patient's disease is arrested and the extrapleural space is obliterated.

Of the 32 patients known to be alive, a minimum of five years after operation,

31 (96.8 per cent) are working (table 4) and 29 (90.6 per cent) discharge no tubercle bacilli in the sputum. Of the 11 who died, 6 were uncoöperative in their treatment and represent inadequate personality assessment. All of the deaths resulted from tuberculosis, with the exception of one diabetic who refused to observe her diet and take insulin regularly, and consequently succumbed in diabetic coma.

TABLE 3

*Status of the extrapleural space after five year minimum*

Extrapleural oleothorax.....	17
Extrapleural space obliterated.....	13
Extrapleural space not obliterated.....	2
Thoracoplasty.....	3
Unknown.....	3

TABLE 4

*Status of the 45 patients after a minimum period of five years after extrapleural pneumothorax*

Working.....	31 or 68.8 per cent
Convalescent.....	1 or 2.2 per cent
Unknown.....	2 or 4.4 per cent
Dead.....	11 or 24.4 per cent

TABLE 5

*Final result attained in 52 extrapleural pneumothoraces*

Dead.....	14 operations
	6 satisfactory (disease ipsilateral lung controlled)
	8 unsatisfactory
Living.....	36 operations
	33 satisfactory (disease ipsilateral lung controlled)
	3 unsatisfactory
Unknown.....	2 operations
Total satisfactory operations.....	39, or 75 per cent

The final analysis of the 52 operations may be seen in table 5. In reviewing the cases, it was found that 6 of the 14 operations performed upon those who died could be classified as satisfactory in controlling the disease of the ipsilateral lung. This conclusion was attained by noting radiographic progression in the contralateral lung, or clinical evidence of extrapulmonary disease sufficient to cause the patient's exitus, while the operative (or ipsilateral) lung remained roentgenographically stable.

## CONCLUSIONS

1. Extrapleural pneumothorax is an effective additional collapse measure in the treatment of pulmonary tuberculosis.

2. The procedure has the advantage of producing little or no thoracic deformity and is a single-stage operation.

3. Extrapleural pneumothorax has the disadvantage of requiring meticulous and prolonged postoperative care which is not suitable for the emotionally unstable or vagrant patient.

4. The complications of extrapleural pneumothorax can be managed by medical means except in a few instances.

## SUMMARY

The indications for operation, the operative technique, and the postoperative management of extrapleural pneumothorax have been reviewed. A report is made of the present status of 45 patients in whom extrapleural pneumothorax was instituted more than five years ago. Thirty-two of the 45 patients are known to be alive and 31 (96.8 per cent) are working. Thirty-nine (75 per cent) of a total of 52 operations are classified as satisfactory.

## SUMARIO

*Neumotórax Extrapleural*

1. En este trabajo discútense las indicaciones operatorias, la técnica quirúrgica y la asistencia postoperatoria en el neumotórax extrapleural.

2. Recálcase la cuidadosa selección de los casos.

3. Enuméranse las complicaciones del neumotórax extrapleural y describíese la manera de atenderlas.

4. Analízase el estado actual de 45 enfermos, en quienes se ejecutó un total de 52 intervenciones hace más de cinco años: 32 de los 45 se sabe que están vivos, y 31 de ellos (96.8 por ciento) se hallan trabajando; 29 tienen esputo negativo; 39 (75 por ciento) de las 52 operaciones se clasifican como satisfactorias.

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## DISCUSSION

JOHN C. JONES<sup>†</sup>

At the meeting of this Society in San Antonio, Texas, in 1941, my associate, Dr. Ambrose S. Churchill, reported on 50 extrapleural pneumothorax operations in 47 patients (3 bilateral extrapleural pneumothoraces), which were done on Dr. F. S. Dolley's and my service at the Olive View Sanatorium between October 1937 and October 1938. I thought it would be of interest to report on the nine year follow-up study of this group of cases, which has been completed by Doctor Churchill within the past month. In this group there was no operative mortality, nor were there any deaths within the first year after operation. Six patients died in the second and third years postoperatively, and 14 more were either dead or lost from observation four to nine years after operation. We might expect then that the majority of deaths occur after the first four years postoperatively. Fifteen (30 per cent) of the 50 extrapleural pockets required conversion to oleothorax, 6 for antisymphysial and 9 for disinfectional purposes. All the patients with persistent fluid in the extrapleural spaces had cultures of the fluid and, in a total of 19 per cent of the series, tubercle bacilli were isolated by culture or guinea pig inoculation. These patients were classified as having tuberculous empyema. In 5 patients, thoracoplasties were completed to obliterate the extrapleural pocket. Two of these patients are cured, two are dead, and one patient has been lost from observation. There remain 6 patients who still have pneumothorax after nine years. Two of this group have active disease, but the remaining 4 are well and are apparently cured of their disease, although their lungs are reluctant to expand to obliterate the space.

In summary, a nine year follow-up of 47 patients with extrapleural pneumothorax reveals: 15 (31.9 per cent) are dead; 5 (10.6 per cent) are lost from observation; 5 (10.6 per cent) still have active tuberculosis; and 22 (46.8 per cent) are apparently cured.

In order to be able to state that extrapleural pneumothorax is a preferable procedure to thoracoplasty, the procedure must be applicable in more cases than is thoracoplasty, the mortality in extrapleural pneumothorax must be less than in thoracoplasty, and the results must be better than in thoracoplasty. As we can safely state that extrapleural pneumothorax meets none of these requirements, it follows that it is not going to replace thoracoplasty as a collapse measure. We believe, however, that there is still a place for extrapleural pneumothorax in our armamentarium, even though as time goes on the indications for it seem narrower and its applicability decreases.

We believe that the judicious application of streptomycin therapy will increase the number of cases improved sufficiently to be thoracoplasty candidates and, by the same token, reduce the numbers of indications for extrapleural pneumothorax. We also hope that, in those cases coming to extrapleural pneumothorax, pre- and postoperative treatment with streptomycin will appreciably reduce the serious complication of tuberculous extrapleural empyema.

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## STREPTOMYCIN IN THE TREATMENT OF TUBERCULOUS SINUSES<sup>1,2,3</sup>

BENJAMIN L. BROCK<sup>4</sup>

At the meeting of this Society in San Antonio, Texas, in 1941, my associate, Dr. Ambrose S. Churchill, reported on 50 extrapleural pneumothorax operations in 47 patients (3 bilateral extrapleural pneumothoraxes), which were done on Dr. F. S. Dolley's and my service at the Olive View Sanatorium between October 1937 and October 1938. I thought it would be of interest to report on the nine year follow-up study of this group of cases, which has been completed by Doctor Churchill within the past month. In this group there was no operative mortality, nor were there any deaths within the first year after operation. Six patients died in the second and third years postoperatively, and 14 more were either dead or lost from observation four to nine years after operation. We might expect then that the majority of deaths occur after the first four years postoperatively. Fifteen (30 per cent) of the 50 extrapleural pockets required conversion to oleothorax, 6 for antisymphysial and 9 for disinfectational purposes. All the patients with persistent fluid in the extrapleural spaces had cultures of the fluid and, in a total of 19 per cent of the series, tubercle bacilli were isolated by culture or guinea pig inoculation. These patients were classified as having tuberculous empyema. In 5 patients, thoracoplasties were completed to obliterate the extrapleural pocket. Two of these patients are cured, two are dead, and one patient has been lost from observation. There remain 6 patients who still have pneumothorax after nine years. Two of this group have active disease, but the remaining 4 are well and are apparently cured of their disease, although their lungs are reluctant to expand to obliterate the space.

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We believe that the judicious application of streptomycin therapy will increase the number of cases improved sufficiently to be thoracoplasty candidates and, by the same token, reduce the numbers of indications for extrapleural pneumothorax. We also hope that, in those cases coming to extrapleural pneumothorax, pre- and postoperative treatment with streptomycin will appreciably reduce the serious complication of tuberculous extrapleural empyema.



tration of streptomycin, which was considered to be caused by the drug. No instance of exfoliative dermatitis was observed.

Transient casts appeared in the urine of 8 of the 12 patients, but no kidney damage of a permanent character was found to be present. The blood urea nitrogen was not elevated in any instance and no evidence of liver damage was demonstrated.

Four of the patients showed an eosinophilia of over 5 per cent which persisted throughout treatment. In most of the group the sedimentation rate was elevated at the beginning and at the end of treatment. The streptomycin concentration of blood serum was between 10 and 20 mcm. per cubic centimeter in all cases.

Soon after the start of streptomycin therapy, 11 of the 12 patients showed outstanding clinical signs of improvement manifested by a sense of well-being, an increase in appetite, and a gain in weight. Some of the Negro patients, who were extremely emaciated and in a critical condition at the time streptomycin therapy was started, rapidly began to gain weight. The average gain was 15 pounds. Those who were febrile at the beginning of therapy quickly became afebrile and remained so except for a few who had febrile reactions from the streptomycin.

Nine of the 60 sinuses closed within one to four weeks, and 9 within six to eight weeks, after streptomycin therapy was started. Thirty sinuses closed between the tenth and twelfth weeks of treatment and 11 (approximately 20 per cent) closed within thirteen to twenty weeks of the start of chemotherapy.

The series has not been followed for a sufficient period to determine whether streptomycin has produced a permanent closure of the sinuses, but the promptness with which they healed following initiation of treatment was outstanding. After about three to four days of streptomycin therapy, the purulent material draining from the sinuses became less purulent and smaller in amount. In some instances, tuberculosis sinuses of several years' duration, originating in bone in the ischio-rectal region, or following appendectomy, have closed within a week to ten days.

Induration surrounding the sinus tracts and the associated tenderness have disappeared as early as one month after treatment was begun.

The fact that closure is more prompt when free drainage is present was impressive. If small abscesses exist under the skin and the sinus is not draining adequately, the area should be incised and the pus evacuated. The area then heals by healthy granulation. Where necrotic bone or cartilage is present, as for example in a rib or sternum, the necrotic material should be removed.

When a large cold abscess exists in conjunction with tuberculosis of the vertebrae, there is little tendency for the pus to disappear under streptomycin therapy, unless it is evacuated by open drainage. Several of the cases have been drained by this method through the groin or the lateral surface of the thigh. One such abscess, which pointed in the back opposite the affected vertebrae, was drained by open incision. When these large open sinuses are allowed to drain at the same time streptomycin is being administered, they fill in quickly with healthy granulation and close. Since closure of such sinuses in this series, there has been no evidence or any recurrence of pus in the paravertebral area or elsewhere. Fol-

lowing drainage of such abscesses, the patient feels greatly improved in the same fashion as after drainage of a nontuberculous abscess.

One of the patients who had unilateral exophthalmos associated with radiographic evidence of marked destruction of the orbital portion of the frontal bone prior to streptomycin therapy, has recently shown radiographic evidence of extensive bone regeneration. As yet, however, there has been little evidence of regeneration of bone along the lateral surfaces of affected vertebrae or in ribs partially destroyed by a tuberculous process. This lack of regeneration has been notable in the case of "punched out" areas in the shafts of long bones.

Of the 60 original draining sinuses, only one continues to drain at this time (March 10, 1947), eight months since streptomycin was started. Even this sinus is showing marked improvement since open drainage of the perineum was instituted on November 18, 1946, and since discontinuance of streptomycin therapy on December 26, 1946. The incised area is healthy in appearance and it is believed it will be completely closed within a short time. Recently a small indurated area over the sternum in another patient, which had not disappeared under streptomycin therapy, was incised. However, no draining sinus was present prior to incision of the area.

Of the other sinuses, the longest time which has elapsed since closure is eight months; the shortest time two months; the average time four months.

#### *Acknowledgments*

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# THE PROPHYLACTIC ADMINISTRATION OF STREPTOMYCIN BEFORE AND AFTER MAJOR THORACIC SURGICAL OPERATIONS<sup>1</sup>

PAUL C. SAMSON<sup>2</sup>

This presentation is a preliminary report. Although valuable information is accumulating, figures of sufficient magnitude to undergo statistical analysis are not yet available. It is obvious, however, that the present studies now under way in Veterans Administration hospitals and elsewhere should continue.

What portion of our present knowledge of streptomycin may be applied to prophylactic therapy in surgery? It is known that streptomycin is tuberculostatic, and that fresh exudative and hematogenous lesions are influenced more favorably than those lesions which are essentially fibrotic or productive in nature.

First, it seems logical that streptomycin may be used to prepare patients for surgery more rapidly than before. For example, freshly reactivated lesions and acute bronchiogenic or hematogenous foci occasionally develop in patients who otherwise might be suitable for major collapse therapy. In these, the administration of streptomycin may be expected to shorten the interval before surgical intervention. Continued observations on cases of this type are being recorded.

Second, the preliminary results of direct prophylaxis can be summarized at this time. The bulk of the material comes from the Veterans Administration under direction of the Central Streptomycin Committee. A brief description of the overall plan should be in order. Originally, 19 study units were set up in Veterans Administration hospitals. In general, every other patient undergoing thoracoplasty has been given streptomycin with the alternate patients serving as controls. Moreover, all patients undergoing pulmonary resection for tuberculosis have received streptomycin. The dosage regimen selected for both groups was 1.8 grams daily in divided doses for one week before and two weeks following each operation. It should be emphasized that this dosage may be changed in the future and that the length and time of administration as related to surgery may be varied as experience is gained. Intrapleural injections of streptomycin may be warranted. It is possible that a longer period of administration postoperatively may be found to be advantageous.

As the course of streptomycin planned for cases of resection and single-stage thoracoplasty was brief, no special laboratory studies were made except in the presence of preëxisting renal disease. During multiple-stage thoracoplasties, with a period of less than six weeks intervening between operations, laboratory procedures chosen to help detect the occurrence of toxic effects have been carried out.

On May 1, 1947, reports had been received from ten Veterans Administration

<sup>1</sup> Presented before the Medical Section, as part of the symposium on *Streptomycin in Surgical Tuberculosis*, at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 18, 1947.

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hospitals (1). During this time 60 patients underwent one or more stages of thoracoplasty without the development of postoperative "spread," reactivation, or empyema. In a parallel series, comprising approximately the same number of thoracoplasty stages, two "spreads" developed. One of these has since completely cleared following the postoperative administration of streptomycin.

Twenty-four patients have undergone pulmonary resection for tuberculosis under streptomycin protection. There have been no "spreads" in this group. Apparently, one empyema developed postoperatively which was associated with a bronchial fistula. It is reported that thoracoplasty will be required in this case.

Glover, Clagett, and Hinshaw (2) have recently reported their experience with the use of streptomycin in 5 cases of pulmonary resection. Penicillin was likewise administered to these patients. In 3, streptomycin was given both pre- and postoperatively; in the 4th and 5th cases, the drug was given postoperatively only. In the 5th case, a "bad risk" pneumonectomy, streptomycin was not available for preoperative administration. A postoperative spread to the contralateral lung was controlled with streptomycin in doses of 1.5 to 2.4 grams daily for a period of three months. The authors conclude that "the results in these five consecutive cases are sufficiently encouraging to warrant the continued trial of combined surgical and antibiotic treatment".

Gebauer and Walker (3) have used streptomycin both pre- and postoperatively in 9 pneumonectomies for tuberculosis since January, 1947. In addition to intramuscular administration, Gebauer instilled 2.0 grams of streptomycin intrapleurally at the time of operation and injected 3.0 grams daily into the pleural cavity for the first five postoperative days. In this series there were no empyemas, positive pleural fluids, nor tuberculous "spreads". In 8 previous resections, without streptomycin, tubercle bacilli were cultured from the pleural fluid of 4 patients, of whom 2 developed late bronchial fistulae and frank empyema. One patient developed a fresh exudative focus in the contralateral lung.

The writer, in collaboration with Doctor Dugan, has used streptomycin as prophylaxis before surgery in 10 patients. In 5 of these, pulmonary resection was performed and none developed either a "spread" or an empyema. These results were obtained despite the fact that in one patient a secondary thoracotomy was necessary one week following resection because of a recurrent bronchiolar fistula which developed on the fissural surface of the upper lobe. The dosage of streptomycin employed in this series was that suggested by the Central Streptomycin Committee. In one pneumonectomy, 1.0 gram of the drug was instilled intrapleurally at operation. In all 5 patients, penicillin in doses averaging 200,000 units in twenty-four hours was used in conjunction with streptomycin both pre- and postoperatively. The impression was obtained that, under streptomycin protection, patients undergoing resection do not have quite the stormy course which frequently has accompanied these operations for tuberculosis in the past. Clinically, they are not so ill; the postoperative fever is less; and the return of temperature to normal is more rapid. In 10 resections for pulmonary

tuberculosis, performed prior to the use of streptomycin, there were 2 empyemas and one fatal postoperative pneumonia which was presumably tuberculous. One of the empyemas, which followed pneumonectomy, has since cleared remarkably following the use of streptomycin. The other 5 patients in whom streptomycin was used comprise a miscellaneous group representing special indications during thoracoplasty, and the excision of a tuberculous abscess of the thoracic wall with tight closure. All of these patients have done exceptionally well following operation.

Tentative conclusions concerning the prophylactic use of streptomycin in thoracic surgery are as follows:

1. In general, operative indications may be extended, as the tuberculostatic action of streptomycin may prevent invasive or progressive infection by tubercle bacilli during and following surgery. This may be roughly compared to experience in the use of penicillin in infected wounds where it has been found possible to extend operative indications in spite of the presence of infection.

2. Streptomycin is probably indicated wherever and whenever tuberculous tissues are actually incised or excised. Limited experience indicates that, within the following surgical categories, most tuberculous patients under streptomycin protection have had a more satisfactory course than would have been expected otherwise. Case records are available to represent nearly all of the following groups:

- a. pulmonary resections;
- b. decortications;
- c. open pneumonolysis if pleural tubercles are demonstrated;
- d. lower stage (Schede-type) thoracoplasties where a sinus track is excised or an empyema cavity actually entered;
- e. cold abscesses of the thoracic wall in which complete excision of tuberculous soft tissue, bone, or cartilage can be accomplished and tight closure of the skin performed;
- f. open cavernostomies with insertion of a skin flap;
- g. pericardiolysis for Pick's disease when the original infection is believed to have been tuberculous.

3. Certain special indications exist such as: extrapleural thoracoplasty; needle-track infections of the thoracic wall; a complicating and persisting ulcerative tracheobronchitis, in which the need for thoracoplasty is sufficiently strong to preclude further waiting for the ulcerative tracheobronchial lesions completely to regress; thoracoplasty (particularly an anterior stage) in the presence of sinus tracks leading to infected bone or cartilage; lower stages of a thoracoplasty in the presence of a tuberculous wound infection; all stages of a thoracoplasty in the presence of a mixed infection empyema; anterior rib resections or anterior thoracoplasty stages prior to the insertion of a Monaldi catheter in patients with balloon cavities. Alexander (4) and Welles (5) have both reported a disproportionate number of "spreads" following the last named procedure compared with the usual number of postthoracoplasty infections. Because of the risk of complications, present expense, and equivocal results to date, it is not believed that

routine protection with streptomycin is necessary or advisable in patients undergoing an uncomplicated extrapleural thoracoplasty, extrapleural pneumonolysis or closed or open pneumonolysis. Complications of these operations such as "spreads," tuberculous wound infections, sinus tracks, bone lesions and, perhaps, empyemas should be treated by streptomycin when they become manifest.

4. No information is available concerning the value of streptomycin in the treatment of tuberculous and mixed infection empyemas. A protocol is now being prepared by the Veterans Administration for an investigation of this problem.

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# INTRAPLEURAL PNEUMONOLYSIS<sup>1,2</sup>

JOSEPH GOORWITCH<sup>3</sup>

This study consists of an analysis of all thorascopies and pneumonolyses, consecutive and unselected, performed by the writer at the Los Angeles Sanatorium from 1944 to 1946, and a review of the available reports published in English from 1943 to 1947. The available English and American literature published prior to 1943 has been reviewed in two previous publications (6, 8).

The Los Angeles Sanatorium series consists of 43 patients. They were subjected to 60 operative stages of intrapleural pneumonolysis. In one patient, both lungs were subjected to operation. Some of the tables, therefore, show the number 44 instead of 43 patients. In 5 additional patients, the procedure was limited to a purely exploratory thoracoscopy because adhesions were considered not feasible for pneumonolysis and in these patients pneumothorax was discontinued without ill effects.

## CLINICAL MATERIAL

The status of the tuberculous infections, immediately prior to operation, in the 43 patients in the series may be seen in table 1.

On roentgenologic examination, all of the pulmonary cavities were in the upper half of the lung field and most of them in the upper lobe; very few were in the apex of the lower lobe. It is significant that, in two-thirds of the patients subjected to pneumonolysis, the disease was bilateral. This probably accounts for the fact that the incidence of sputum and/or gastric contents containing tubercle bacilli was greater than the incidence of roentgenologic evidence of cavitation in the homolateral lung.

## THORACOSCOPY AND PNEUMONOLYSIS

The two-cannula technique with the Coryllos pneumonolysis set, employing galvanocautery, was used throughout the 60 operative stages upon the 44 lungs of 43 patients. Adhesions were freed flush with the chest wall rather than cut or severed. The type of operation and the nature of the adhesions may be seen in tables 2 and 3.

By complete pneumonolysis is meant a pneumonolysis in which there is complete freeing of all adhesions attached to the disease-bearing lobe. An incomplete pneumonolysis consists of complete freeing of some adhesions and leaving others intact. The term, partial pneumonolysis, is used to designate the partial freeing of some or all of the adhesions.

## OPERATIVE AND POSTOPERATIVE COMPLICATIONS

As in previous publications (5, 8), postoperative complications encountered within the first four postoperative weeks were regarded as attributable to the

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**TABLE 1**  
*Immediate preoperative status of the 48 patients*

Sex:		
Males.....		23
Females.....		20
Age:		
Range.....		16 to 53
Average.....		31
Extent of pulmonary tuberculosis (National Tuberculosis Association Diagnostic Standards)		
Moderately advanced.....		22
Far advanced.....		21
Tubercle bacilli in sputum or gastric contents:		
Demonstrated		
Concentration.....	30	} 33
Culture only.....	3	
Not demonstrated (but previously demonstrable)		
Concentration only.....	2	} 10
Culture.....	8	
Bronchoscopy:		
Normal.....		3
Erythema only.....		1
Fever:		
Absent.....		38
Present (100 to 101°F.).....		5
Contralateral lung:		
Clear.....		15
Infiltration only (collapsed by pneumothorax in 3 cases).....		23
Patent excavation.....		6
Lungs operated upon (44):		
Right.....		21
Left.....		23
Duration of pneumothorax:		
Range.....	1½ to 21 months	
Average.....	9 months	
Roentgenographic evidence of cavitation:		
Present		
Pre-pneumothorax.....		41
Preoperative.....		30
Absent		
Pre-pneumothorax.....		3
Preoperative.....		14
Size of pulmonary cavities (the greatest diameter):		
Range.....	1 to 8 cm.	
Average.....	3 cm.	
3 cm. or less.....		27
Over 3 cm.....		7
Pleural effusions (excluding minimal transient effusions occupying bottom of costophrenic sinus):		
Absent.....		33
Present		
Small serous.....	7	} 11
Moderate serous.....	4	
Obliterative pleuritis:		
Absent.....		43
Present.....		1



operative intervention, and those encountered after this period as not attributable to the operation. For the rationale of this arbitrary classification, the reader is referred to the previous reports.

The various complications encountered may be seen in table 4.

In calculating the incidence of operative and postoperative complications, fever below 100° F. or lasting less than one week, and small transient pleural effusions occurring alone, were not regarded as complications because they have no clinical significance.

TABLE 2  
*Type of operation*

Complete freeing.....	20 stages
Incomplete freeing.....	6 stages
Partial freeing.....	34 stages

TABLE 3  
*Adhesions subjected to operation*

Type:	
Strings.....	66
Cords.....	65
Bands.....	121
Number per lung:	
Range.....	1 to 16
Average.....	6
Attachments:	
Visceral	
Upper lobe.....	37
Lower lobe.....	7
Parietal	
Posteriorly on chest wall.....	36
Laterally on chest wall.....	21
Anteriorly on chest wall.....	20
Extreme apex on chest wall.....	8
Great vessels.....	3

The single instance of spontaneous pneumothorax occurred three months postoperatively and, from the description of the circumstances, must have been on a purely traumatic basis. Aspiration of air was followed by complete recovery. The single instance of intrapleural hemorrhage occurred nine months postoperatively and was not readily explainable. The pneumothorax was abandoned two months later following aspirations first of blood and later of serous fluid.

Moderate or persistent serous pleural effusions occurred in 2 patients who were free of effusion preoperatively. In the first patient with a negative sputum and no roentgenologic evidence of cavitation at the time of operation, a total of 650 cc. of serous fluid was aspirated during the first month following a partial pneu-

monolysis. Recovery was uneventful. In the second patient, the sputum contained tubercle bacilli, a large pulmonary cavity was present, and serous pleural fluid totaling 400 cc. was aspirated four months following a complete pneumonolysis. An obliterative pleuritis eventually developed. When this patient was discharged twenty-three months postoperatively, the sputum contained no tubercle bacilli and there was no roentgenologic evidence of cavitation.

The patient, who developed a serous pleural effusion one and one-half months following a fairly extensive, partial, two-stage pneumonolysis, had a positive sputum and roentgenologic evidence of cavitation. The serous fluid was aspirated, lung reexpansion was encouraged, and a homolateral phrenic crush

TABLE 4

*Operative and postoperative complications (60 stages on 44 lungs of 43 patients)*

COMPLICATIONS	INCIDENCE		
	Within first four postoperative weeks and attributable to operation	After first four postoperative weeks and not attributable to operation	
	Number	Number	Months post-operative
Absent.....	55		
Present.....	5		
Prolonged fever.....	5		
Spontaneous pneumothorax.....	0	1	3
Intrapleural hemorrhage.....	0	1	0
Moderate serous pleural effusion.....	1	1	4
Tuberculous empyema.....	0	1	1½ to 6
Pyogenic empyema.....	2	0	—
Extension of pulmonary tuberculosis.....	1	1	5
Obliterative pleuritis.....	0	3	10-18
Cessation of respiration.....	1		

Severe subcutaneous emphysema, massive serous pleural effusions, bronchopleural and pleurocutaneous fistulae, mixed tuberculous empyema, loss of pneumothorax space, air embolism, nerve injury, and death complicating operation did not occur.

was done. The fluid became purulent six months postoperatively, at which time tubercle bacilli were demonstrable in the fluid on smear and culture. No other microorganisms were cultured from this fluid. Fourteen months postoperatively, when the patient was discharged, her sputum revealed no tubercle bacilli on concentration or culture, roentgenologic evidence of cavitation was absent, and her general condition was good, although small amounts of purulent fluid could be aspirated at two week intervals.

The 2 patients in whom pneumonolysis was complicated by nontuberculous pyogenic empyema were operated upon within four days of each other. Repeated examinations of the pleural exudate from both patients failed to reveal tubercle bacilli. In neither patient was intrapleurally injected dye recovered in

the sputum, thus demonstrating the absence of a macroscopic bronchiopleural fistula. Such a fistula might have followed direct operative trauma to the lung or a postoperative tear or slough of a tuberculous pulmonary focus. It is possible, therefore, that the infection was exogenous, perhaps originating in the operator's nasopharynx, rather than a consequence of contamination of the pleural cavity through trauma to the lung. In both patients, tubercle bacilli were abundant in the sputum, both showed roentgenologic evidence of cavitation and, in both, complex band adhesions were freed only partially. Both patients became febrile immediately after operation and promptly developed a serous effusion which became purulent during the ensuing month. Treatment consisted of frequent aspirations of fluid without replacement with air, in an attempt to encourage lung reëxpansion, and penicillin injections both intrapleurally and intramuscularly. During the first postoperative month thoracocentesis of both of these patients with empyema yielded a total of about 2 liters of serous fluid and  $3\frac{1}{2}$  liters of purulent fluid. Both patients responded by obliteration of the pleural cavity which was accompanied by clinical improvement manifested by defervescence and gain in weight. The patient with the smaller cavity and unilateral disease also achieved sputum conversion and cavity closure. Three months postoperatively, a homolateral phrenic crush was performed on this patient in order to achieve some relaxation of the adhering lung. The patient with the larger cavity and contralateral infiltration developed some further increase in the amount of infiltration and both the cavity in the homolateral lung and the bacillary content of the sputum remained unchanged. When he left the sanatorium seven months postoperatively, his general condition was no worse than it had been before operation.

Contralateral extension of pulmonary tuberculosis occurred in 2 patients, one of whom has just been mentioned as having also developed a nontuberculous pyogenic empyema. The second patient showed a contralateral spread five months following an uneventful 2-stage pneumonolysis and one month after voluntary cessation of an ineffective pneumothorax. Despite an anatomically perfect pneumothorax resulting from pneumonolysis and negative bronchioscopic findings, the cavity persisted within the atelectatic upper lobe and tubercle bacilli persisted in the sputum.

Complete cessation of respiration occurred shortly after operation was begun in a patient whose general condition was poor, who had extensive bilateral pulmonary excavation, and whose only chance, slim as it was, lay in collapse by pneumothorax. The customary preoperative nembutal resulted in such sedation that additional opiates were omitted. When it was noted that pulmonary motion ceased, the trocars were withdrawn and the usual stimulants administered. Shallow respirations returned promptly and the drowsiness wore off in about two hours. At a later date, following a smaller dose of the same sedative, an uneventful attempt at pneumonolysis was made. Inasmuch as sufficient freeing to improve the type of collapse was not feasible, however, the pneumothorax was discontinued as useless. When the patient left the sanatorium one year postoperatively, his condition was no worse than before operation.

It should be emphasized that the longer the follow-up, the greater the list of complications of pneumothorax not attributable to pneumonolysis. The complications just described, most of which were regarded as nonattributable to pneumonolysis, were presented simply for the sake of completeness.

#### POSTOPERATIVE FOLLOW-UP

Postoperative follow-up ranged from seven to thirty-one months and averaged twenty months. There were three deaths in this series. All were unrelated to the operation and the interval between operation and death ranged from thirteen to twenty months. One death was due to intravenous anesthesia in the course of another procedure, the second to a massive pulmonary hemorrhage in a patient with bilateral pulmonary excavation, the third to extensive pulmonary "spread"

TABLE 5

*Status of the pneumothorax following operation (44 lungs)*

Maintained.....	30
Discontinued because of	
{ Ineffectiveness.....	8
Empyema.....	3
Obliterative pleuritis.....	2
Voluntary cessation.....	1
	14

TABLE 6

*Anatomical results of pneumonolysis (44 lungs)*

Incomplete and partial freeing (obviously insufficient to justify the expectation of change in status of collapse).....	5*
Incomplete and partial freeing.....	19
Complete freeing.....	20

\* In 4 patients pulmonary excavation was bilateral.

in a patient with bilateral pneumothorax and residual cavitation, despite an anatomically perfect pneumothorax.

Additional collapse measures such as phrenic crush, pneumoperitoneum, and thoracoplasty on the homolateral or contralateral side, were carried out at some time postoperatively in a small number of patients. In some instances, it must be pointed out, these accessory procedures were added to a clinically good result obtained following a partial pneumonolysis. In other patients, these additional collapse measures were instituted because the clinical results of pneumonolysis were not satisfactory. Several patients were bronchoscoped at some time postoperatively as indications arose, but only one was found to have developed a progressing stenosis of a stem bronchus. This patient failed to attain sputum conversion, but there was no evidence of patent cavitation in the lung, either by roentgenography or by gross examination of the resected lung.

The status of the pneumothorax postoperatively and the anatomical results of pneumonolysis may be seen in tables 5 and 6. In evaluating the results of

pneumothorax following pneumonolysis, the entire series of 43 patients cannot be considered for obvious reasons. For example, in calculating the incidence of cavity closure, those patients who preoperatively had no evidence of cavity in the collapsed lung must be excluded. Moreover, in calculating the incidence of sputum conversion, those with negative sputum preoperatively, as well as those with a contralateral or extraparenchymal source of tubercle bacilli, must be excluded. And in calculating both of these phenomena, it is necessary to exclude the 5 patients who had very extensive adhesions which were obviously freed

TABLE 7  
*Cavity status (44 lungs of 43 patients)*  
*(Body section films frequently used)*

Closed preoperatively.....	14	}	*
Patent (obviously insufficient operative freeing to justify expectation of change in status of collapse).....	5		
Closed ( $\frac{1}{2}$ to 11 months postoperatively).....	21		
Patent.....	4		

\* For reasons given in the text, this portion of the series is excluded in calculating the incidence of cavity closure and sputum conversion.

TABLE 8  
*Sputum status (43 patients)*  
*(By culture of sputum and/or gastric contents)*

Negative preoperatively.....	10	}	*
Unconverted because of:			
Contralateral cavitation..... (7)	10		
Obviously insufficient freeing to justify expectation of change in collapse status..... (5)**			
Homolateral tuberculous bronchitis..... (1)			
Tuberculous tonsillitis..... (1)			
Converted ( $\frac{1}{2}$ to 11 months postoperatively).....	19 (53%)		
Unconverted.....	4 (17%)		

\* For reasons given in the text, this portion of the series is excluded in calculating the incidence of cavity closure and sputum conversion.

\*\* In 4 patients contralateral cavitation was present too.

insufficiently to justify the expectation of a change in the status of the collapse. The respective incidences of cavity closure and sputum conversion may be seen in tables 7 and 8.

Pneumonolysis was complete in 2 of the 4 patients who failed to close cavity and convert sputum after pneumonolysis. In the other 2, it was incomplete but regarded as anatomically fairly satisfactory. Only one of these patients was bronchoscoped and no abnormality was found. Nevertheless, bronchial element was the probable cause for clinical failure in the presence of what appeared to be anatomically satisfactory collapse. Of the 21 patients, in whom cavity closure was achieved, pneumonolysis was complete in 10 and partial in 11. In 5 of this

group, pneumothorax was discontinued. Of the 19 patients whose sputum became converted after pneumonolysis, operation was complete in 11 and partial in 8. In 6 patients of this group, pneumothorax was discontinued.

## REVIEW OF LITERATURE

In a recent review (8) of the available English and American literature on intrapleural pneumonolysis published up to 1943, the writer has discussed and

TABLE 9  
*Incidence of complications attributable to pneumonolysis*

COMPLICATIONS	COLLECTED SERIES OF 8,611 PATIENTS (1924 TO 1947)	GOORWITCH	
		Olive View Sanatorium, 48 patients (1941 to 1942)	Los Angeles Sanatorium, 43 patients (1944 to 1946)
	Range of incidence	Incidence	
	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
Absent.....	27 to 89	89	92
Present.....	11 to 73	11	8
Prolonged fever.....	0 to 13	3.6	8
Severe surgical emphysema.....	0 to 20	1.8	0
Intrapleural hemorrhage:			
Small.....	0 to 100	0	0
Moderate or large.....	0 to 100	1.8	0
Serous effusions:			
Small.....	0 to 93	5.4	—
Moderate or large.....	0 to 33	3.6	1.6
Spontaneous pneumothorax.....	0 to 12	0	0
Bronchopleural fistula.....	0 to 80	0	0
Empyema:			
Uncomplicated tuberculous.....	0 to 24	0	0
Nontuberculous pyogenic.....	0 to 6	0	3.3
Mixed.....	0 to 23	0	0
Obliterative pleuritis.....	0 to 11	0	0
Loss of pneumothorax.....	0 to 10	0	0
Air embolism.....	0 to 1.1	0	0
Pleurocutaneous fistula.....	0 to 8	0	0
Extension of pulmonary tuberculosis.....	0 to 6	0	1.6
Nerve injury.....	0 to 1.6	0	0
Shock.....	0 to 2	0	1.6 (?)
Death.....	0 to 100	0	0

tabulated the pertinent data. The present study brings the review of available literature to January, 1947, (1, 2, 16, 8, 19, 12, 10, 11, 13), thus adding 1,502 cases and making a total of 8,702 collected cases.

In this collected series of 1,502 cases of intrapleural pneumonolysis, the incidence of minimal pulmonary tuberculosis ranged from zero to 14 per cent, that

of moderately advanced from 22 to 41 per cent, and that of far advanced from 54 to 77 per cent. The incidence of positive sputum ranged from 73 to 95 per cent. Two-cannula technique and glavanocautery were used throughout. Among the more common operative and postoperative complications attributable to the operation and reported with their incidence were the following: small intrapleural hemorrhage, 1.2 to 4 per cent; large intrapleural hemorrhage, zero to 2.3 per cent; spontaneous pneumothorax, zero to 4 per cent; bronchopleural fistula, zero to 2 per cent; small serous effusion, 5.5 to 40 per cent; large serous effusion, 3 to 23 per cent; uncomplicated tuberculous empyema, zero to 5.5 per cent; nontuberculous pyogenic empyema, zero to 1 per cent; mixed tuberculous empyema, zero to 2 per cent; loss of pneumothorax space, zero to 2 per cent; death, zero to 8.7 per cent. Ten of the 13 deaths reported were due to empyema which usually followed operative trauma to the lung, often with the production of a bronchopleural fistula. Following pneumonolysis, collapse was reported as

TABLE 10  
*Results of pneumothorax therapy following pneumonolysis*

	STATUS OF (IN PER CENT)					
	Collapse		Cavity		Sputum	
	Com- plete	Incom- plete	Closed	Patent	Con- verted	Uncon- verted
Collected series:						
5,066 patients (1933-1943).....	52	48	72	28	73	27
1,502 patients (1943-1947).....	56	44	—	—	73	27
Olive View Sanatorium, 48 patients (1944).....	55	45	76 <sup>1</sup>	24 <sup>1</sup>	76 <sup>2</sup>	24 <sup>2</sup>
Los Angeles Sanatorium, 43 patients (1947).....	51	49	84 <sup>3</sup>	16 <sup>3</sup>	83 <sup>4</sup>	17 <sup>4</sup>

<sup>1</sup> Calculated on the basis of 34 cases with patent cavitation preoperatively.

<sup>2</sup> Calculated on the basis of 21 cases with positive sputum preoperatively.

<sup>3</sup> Calculated on the basis of 25 cases with patent cavitation preoperatively.

<sup>4</sup> Calculated on the basis of 23 cases with positive sputum preoperatively.

complete in 26 to 72 per cent, and sputum conversion occurred in 66 to 83 per cent. The incidence of cavity closure was specifically stated by two writers only and these reported it to be 76 per cent and 78 per cent, respectively.

In studying the incidence of operative and postoperative complications attributable to intrapleural pneumonolysis, as presented in table 9, it should be realized, that the maximum incidence of complications occurred during the first decade after the introduction of the procedure by Jacobacus. With the greater experience attained in recent years, the incidence of complications is appreciably lower. Just as in the case of any surgical procedure, the incidence of complications will depend, on one hand, on the quality of clinical material available and, on the other, on the clinical judgment and surgical skill of the operator.

The results of pneumothorax therapy following pneumonolysis, like operative and postoperative complications, depend on the clinical material available as well as on the clinical judgment and operative skill of the surgeon. In table 10

may be seen a comparison between results gathered from the literature reviewed and those obtained by the author.

As pointed out in a previous report (8), operative and postoperative complications and alterations in the anatomical character of the collapse are the only results of pneumonolysis. Changes in the status of the pulmonary cavity and of the sputum are strictly the results of the pneumothorax therapy maintained after pneumonolysis. The criteria of cavity closure and sputum conversion for the series collected from the literature were not always stated; those of the writer were given above, as well as in an earlier publication (8). The uniformity with which the incidence of cavity closure and sputum conversion is found to be greater than the incidence of complete pneumonolysis provides definite proof that satisfactory clinical results are obtainable following the improvement in the anatomical character of the collapse which may result even from a partial or incomplete pneumonolysis. Complete and anatomically perfect pneumonolysis is usually, but not always, followed by clinically successful pneumothorax. Occasionally, however, patency of cavity may persist due to a ball-valve block in the bronchus involved.

#### DISCUSSION AND CONCLUSIONS

The indications for intrapleural pneumonolysis depend on the recognition of the rôle played by pleural adhesions in pneumothorax collapse therapy. This rôle has three distinct aspects which require consideration: (1) the relationship between pleural adhesions and complications of pneumothorax; (2) the relationship between pleural adhesions and the time consumed in achieving cavity closure and sputum conversion; and (3) the relationship between pleural adhesions and stability of pulmonary lesions after voluntary cessation of pneumothorax therapy. These three aspects will be discussed individually.

It is generally admitted that the most serious complications of induced pneumothorax, such as spontaneous pneumothorax, air embolism, bronchopleural fistula, and massive serous and purulent pleural effusions, are far more common in the presence of adhesions than in their absence (2, 7, 17, 18). If this is accepted as the truth, and if it is demonstrated that complications of thoracoscopy and pneumonolysis are no more common or serious than those of pneumothorax with adhesions, then the mere presence of restraining adhesions should be regarded as an early indication for thoracoscopy and for pneumonolysis whenever feasible. Nontuberculous pyogenic empyema, such as was encountered in the present series, could probably be prevented by the routine use of penicillin pre- and postoperatively. The drug should be administered by the intramuscular route, as well as by intrapleural instillation, at the conclusion of the operation and postoperatively.

It cannot be denied that early cavity closure and sputum conversion are advantageous. In fact, these are the very objectives of induced pneumothorax itself. Likewise, no one will dispute that cavity closure and sputum conversion occur sooner in the absence of adhesions than in their presence. Consequently, the presence of patent cavitation and/or sputum which contains tubercle bacilli,



in association with restraining adhesions, must be accepted as an indication for early thoracoscopy and pneumonolysis, if feasible. Following early pneumonolysis, complications are no greater and results are no worse than following a long delayed operation. In fact, complications are fewer and the results are better following an early operation (8).

There are a few reports in the literature which seem to indicate that the post-pneumothorax stability of pulmonary lesions was greater in patients whose pneumothorax had been uncomplicated by adhesions than in patients whose collapse had not been anatomically perfect. In 1942, Hurst and Schwartz (9) reported upon a series of 117 patients observed for an average of four years after voluntary cessation of collapse therapy. No reactivation of disease occurred among those whose pneumothorax was anatomically perfect, but there were relapses among those whose pneumothorax had been restrained by adhesions. In 1939, two Danish workers reported upon a group of 191 patients observed for five years after reexpansion. The incidence of satisfactory results was twice as high in patients whose pneumothorax had been free of adhesions as in those in whom the pneumothorax had been complicated by adhesions (10). In 1922, Jacobacus was of the same opinion regarding the value of his procedure when viewed from a long range point of view (10). If these observations are accepted as true, there is a third reason for an early attempt to render all pneumothoraces anatomically perfect if thoracoscopy indicates that this can be accomplished with a reasonable degree of safety.

The contraindications to thoracoscopy and pneumonolysis are well recognized. They are: a pneumothorax space not large enough for manipulation of instruments, acute febrile pleural effusion, tuberculous or other pyogenic empyema, and progressing obliterative pleuritis.

Review of the literature indicates a general agreement among phthisiologists that only thoracoscopy can determine whether adhesions are operable (6, 8, 12, 13, 17, 18). At times, even thoroscopic inspection of adhesions does not supply the final answer as to their operability. When in doubt one should not operate unless nothing can be offered the patient except a pneumonolysis. Reports from those who practise routine thoracoscopy on all pneumothorax patients indicate that the procedure is innocuous and that the only sequelae to be expected are low-grade fever and small transient effusions (12, 13). It is possible, in inserting a trocar through the chest wall, to injure the intercostal vessels or to plunge the trocar into the lung. However, these accidents must be extremely rare. In a series of 372 thorascopies without pneumonolysis, collected from the available American and English literature of 1943 to 1947 (1, 2, 6, 10, 11, 12, 13), the complications were reported to be negligible and consisted of low-grade fever, transient pleural effusions, or obliterative pleuritis.

In the opinion of the writer, the introduction of a trocar into the pleural space carries less risk than the introduction of a needle, either to establish a pneumothorax or to administer a refill, particularly as there is now general agreement that, when pneumothorax is attempted, the visceral pleura is usually punctured. The difficulty lies in the apparent simplicity of pneumothorax. At Olive View Sanatorium, for example, during the five-year period ending in 1941, the following

were some of the complications recorded in pneumothorax patients not subjected to thoracoscopy or pneumonolysis: 19 air emboli, 5 of which were fatal; 68 spontaneous pneumothoraces, 7 of which were fatal; and 19 bronchopleural fistulae, 11 of which were fatal. At the same institution, after 73 thorascopies, in which pneumonolysis was not performed, there were no serious complications (6).

Pneumonolysis is far from being innocuous; on the contrary, its dangers are potentially great (5, 8), certainly greater than those of modern thoracoplasty, especially when clinical judgment and surgical skill are deficient. As the available literature is reviewed, however, it becomes evident that the incidence of serious operative and postoperative complications is not greater than the complications which may follow persistent pneumothorax, accompanied by adhesions.

In conclusion, the objectives of thoracoscopy and intrapleural pneumonolysis are as follows: (1) to reduce the incidence of complications of anatomically imperfect pneumothorax; (2) to hasten cavity closure and sputum conversion, thus preventing hemoptysis, bronchogenic spread, and other sequelae of open tuberculosis; and (3) to increase the stability of the pulmonary lesions after voluntary cessation of collapse. Thoracoscopy need not be performed routinely in all cases of pneumothorax. Moreover, adhesions to apparently uninvolved pulmonary lobes do not need to be severed if tubercle bacilli are not demonstrable in the sputum. Nevertheless, there should be greater and earlier application of thoracoscopy in those pneumothoraces which present adhesions to the lesion-bearing lobe regardless of cavity or sputum status, a patent cavity in the collapsed lung, or the persistent discharge of tubercle bacilli of unknown source in the sputum.

#### SUMMARY

The complications and results of thoracoscopy and intrapleural pneumonolysis and postoperative pneumothorax, performed at the Los Angeles Sanatorium, have been analyzed. In addition, the available literature, published from 1934 to 1947, which includes a total of 8,659 patients subjected to pneumonolysis, is reviewed. Thoracoscopy and intrapleural pneumonolysis are essential in the proper management of induced intrapleural pneumothorax, and the indications and contraindications for these procedures are presented. Thoracoscopy and pneumonolysis can be made less hazardous than maintenance of anatomically inadequate pneumothorax. Conversion of anatomically inadequate into anatomically adequate pneumothorax will both prevent most of the complications of pneumothorax and ensure an immediate and long-range control of the disease. In patients with anatomically inadequate pneumothorax, in whom pneumonolysis is not feasible, cessation of pneumothorax followed by other and more effective collapse procedures is indicated.

#### SUMARIO

##### *Pneumonolisis Intrapleural*

Analizanse las complicaciones y resultados de la toracoscopia y la neumonolisis intrapleural y del neumotórax postoperatorio en el Sanatorio de Los Angeles a

la vez que se repasa la literatura disponible, publicada de 1934 a 1947, que comprende un total de 8,659 enfermos sometidos a la neumonolisis. La toracoscopia y la neumonolisis intrapleural resultan indispensables en la asistencia adecuada del neumotórax intrapleural provocado y se presentan las indicaciones y contraindicaciones de las mismas, pudiendo convertírselas en menos peligrosas que lo que sería el mantenimiento de un neumotórax anatómicamente inadecuado. La transformación de un neumotórax anatómicamente inadecuado en anatómicamente adecuado impedirá la mayor parte de las complicaciones del neumotórax y asegurará la cohibición inmediata y a largo plazo de la enfermedad. En los enfermos con un neumotórax anatómicamente inadecuado, en los que no resulta factible la neumonolisis, está indicado el cese del neumotórax seguido de otras y más eficaces técnicas de colapso.

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# BAGASSOSIS

## A Review

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### DEFINITION

Bagasse is the name given the fibrous residue resulting from the crushing of sugar cane and the expression of its juices. Originally the term was applied in Provence, France, to refuse from olive oil mills, and came to mean anything worthless. In Spanish-speaking countries, the term is spelled bagasaosis, or bagazo. In the United States, with Louisiana the leading State in the sugar industry, the French spelling of bagasse is used.

Pulmonary involvement due to inhalation of the dried material (bagasse dust) has given rise to a clinical entity known as bagassosis.

### INDUSTRIAL USES AND COMPOSITION OF BAGASSE

Because of the toughness and insulating properties of its fibers, bagasse is used for making boards for interior decorating and for acoustic and thermal insulating purposes. Recently its use has extended to the manufacture of refractory brick (which resulted in cases of bagassosis occurring in Missouri).

TABLE 1

*Approximate chemical composition of tissues of Louisiana purple cane (basis of percentage of dry matter)*

CONSTITUENT	PITH	BUNDLES	RIND
	per cent	per cent	per cent
Ash.....	1.68	3.58	1.64
Fat and wax.....	0.41	0.72	0.98
Protein.....	1.94	2.00	2.19
Pentosans.....	32.04	28.67	26.93
Cross and bevan cellulose.....	49.00	50.00	51.00
Legnin (by difference).....	14.93	15.03	17.26

TABLE 2

*Approximate chemical composition of Louisiana purple cane bagasse*

CONSTITUENT	PER CENT
Cellulose.....	55
Xylan.....	20
Araban.....	4
Lignin.....	15
Acetic acid.....	6

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The approximate chemical composition of tissues of Louisiana purple cane and Louisiana purple cane bagasse, may be seen in tables 1 and 2.

Bagasse dust consists of pith particles for the most part, mixed with some bundle and rind fibers. There may be some variation in chemical analyses of samples of bagasse, depending upon variety and agronomic factors, *e.g.*, soil, et cetera.

Studies by other workers and from this laboratory disclose that bagasse yields from 3 to 4 per cent ash. Total silica was found to be 50 per cent of the ash. Chemical and X-ray diffraction analysis of the ash yields 3 to 5 per cent silica (quartz). Hence, it is improbable that any etiology based on silica could be established in the handling of bagasse. In fact, had the ash proved to be 100 per cent silica, it would still be regarded as a nuisance dust. It is of further interest to point out that, in all the cases of bagassosis that have been reported, the source of the sugar cane has been Louisiana. The cases described in England arose from bagasse that was shipped there in bales from Louisiana. The writer has been informed that in Hawaii, the Philippines, Cuba, and Puerto Rico, the bagasse is burned for fuel.

#### REVIEW OF PREVIOUS CASES

Jamison and Hopkins (2) described in 1941 the case of a 20-year-old Negro laborer who was employed unloading bagasse from a ship at a board-making factory. This was such a dusty environment that, although a respirator was worn, some dust seeped in and was inhaled. Within four months after employment at this job, the patient experienced an acute onset of fever (103.2° F.), cough with blood-tinged sputum on several occasions, and dyspnea on slight exertion and after coughing. Physical examination revealed coarsened breath sounds and râles at the lung bases posteriorly. A chest roentgenogram on admission was interpreted by the roentgenologist as showing bilateral pneumonia. Four days later, repeat roentgenograms were taken which showed miliary mottling throughout both lungs, similar to the densities characteristically seen in miliary tuberculosis. However, intradermal tuberculin tests were all negative. Examination of concentrate from a twenty-four hour and a forty-eight hour total specimen of sputum revealed no acid-fast bacilli, although a fungus was obtained by culture. The authors failed to state the nature of the fungus. In the course of two months, the roentgenographic picture returned to normal and the patient became symptom-free. During the period when the patient was febrile and dyspneic, he was treated with inhalations of carbon dioxide and oxygen and a sedative cough medicine. A course of 10.0 grams of sulfapyridine was given, which had no effect on the temperature.

Castleden and Hamilton-Paterson (3), in 1942, reported four cases of bagassosis. One was a young man 19 years of age, who, after six weeks of feeding bales into the breaking-machine, developed increasing dyspnea, cough with scanty sputum that was sometimes blood-tinged, and a fever of 100.6° F., which lasted for a week. The findings on physical examination consisted of impaired

percussion with distant bronchial breathing at both bases and diminution of vocal fremitus and vocal resonance at the right base. Râles were present at the right base and fine scattered crepitations were heard in all other areas. An outstanding feature was the presence of cyanosis with extreme dyspnea which persisted for three weeks. The dyspnea, which never had an asthmatic quality, was markedly relieved by oxygen, which was administered continuously by nasal catheter for fifty-one days. Sulfapyridine had no influence on the course of the disease. A chest roentgenogram, taken on admission, suggested bilateral bronchopneumonia. A repeat roentgenogram, taken forty-five days later, showed an increase in the area of consolidation. Finally, sixty-one days after admission, coinciding with symptomatic relief, the chest began to clear and the abnormal findings disappeared. It is interesting to note that the scanty mucopurulent sputum contained *M. catarrhalis*, *Str. viridans*, and fusiform bacilli, but no tubercle bacilli. The cells in the sputum were epithelial, polymorphonuclear, and lymphocytic. No eosinophiles were present. Moreover, the blood picture did not reveal any eosinophiles.

The second case which these authors presented occurred in an electrical mechanic, 37 years of age, who, although not directly engaged in the work of breaking the bales, spent considerable time in this area making repairs. This man developed the same train of symptoms as the patient described above, *i.e.*, dyspnea, cough, scanty sputum. On admission in 1940, he showed no abnormality beyond a catarrhal bronchitis. Roentgenograms taken nearly a year later showed appearances very much like bilateral pulmonary tuberculosis. The patient continued to develop an extensive progressive fibrosis of both lungs. He died in 1944 and necropsy revealed a contracted, airless and fibrotic upper lobe of the left lung. There was considerable bronchiectasis with a few bronchiectatic cavities up to 1.0 cm. in diameter, which were empty and had smooth grey linings. Bronchioles were thickened and dilated up to 0.3 cm. diameter throughout the anterior third of the left upper lobe and throughout the lower lobes of both lungs and the right middle lobe. The intervening areas consisted of well aerated emphysematous lung tissue. There were large areas of severe emphysema with emphysematous bullae at all borders of the lower and middle lobes of both lungs. There were large areas of fibrotic pneumonia throughout and the visceral pleura covering both lungs contained numerous areas of fibrous thickening. Fibrous pleural adhesions obliterated both pleural cavities except over part of the left lower lobe.

The third case developed dyspnea, scanty sputum and cough after one month's work at the bale-breaking machine. Roentgenogram of the chest demonstrated no lung lesions.

The fourth case developed dyspnea, cough and scanty sputum after sixteen months of work at the bale-breaker. A roentgenogram revealed a general streaky opacity throughout both lungs. This patient improved upon being transferred to outdoor work.

Gillison and Taylor (4) reviewed four cases of bagassosis, two of which were

also reviewed by the authors previously cited. Gillison and Taylor summarize their findings as follows:

"1. Each man showed an 'incubation period' of approximately the same length, as the time of exposure to bagasse dust before the onset of acute symptoms was from 2 to 4 months in all cases.

2. The acute phase of the illness was of sudden onset, *i.e.*, one was riding home on the bicycle feeling quite well, when 20 yards from his door, he suddenly felt 'winded', started coughing violently, reaching home with difficulty. Another at work 'suddenly felt a tightening feeling across the front of the chest, and a severe hacking cough came on.'

3. The cough was particularly violent and continuous for several days.

4. The sputum was described as 'dark and looked and tasted like rotted bagasse'. 'Green, blue and dirty with a foul smell.' 'Dark and yellow with a burning taste.' 'Like manure.'

5. Three men described severe retrosternal pain coincident with the onset of cough and dyspnea.

6. All patients complained of great weakness, which continued for months.

7. Less specific but equally marked, were mental depression and loss of weight and appetite.

8. In only one case was there decided X-ray evidence of disease. This consisted of general increase in striations in both lungs, the appearance being suggestive of silicosis in the reticular stage.

9. Bronchoscopic examination showed abnormal congestion of the trachea and bronchi, excessive white frothy mucous, glazing of mucosa more marked than normal. The bronchoscopic swabs showed no molds."

In 1944, Jamison, Bryan and Day (5) reported another case in a 32-year-old Negro who was engaged for a month moving bagasse from the fields to railroad cars for shipment. He developed dyspnea, cough and scanty clear mucoid sputum and fever. The sputum failed to reveal tubercle bacilli or any fungi. A roentgenogram, taken on admission, revealed miliary-like infiltration throughout both lung fields. There was also enlargement of both hilar regions. On the twenty-fourth hospital day, the lung fields started to clear and resolution was completed in the course of four months.

Sodeman and Pullen (6, 7), reported 11 additional cases. They point out that dyspnea was invariably the chief complaint, but that a cough with scanty, mucoid sputum was an early and important symptom. In their cases, intermittent fever rising to 102° F. was observed up to three or four weeks. Roentgenograms showed characteristic miliary mottling throughout both lung fields, especially in the hilar areas. In 10 cases, polymorphonuclear leucocytosis occurred. A section of lung obtained at necropsy showed a fibroblastic reaction of the interstitial tissue. Spicules were not numerous, but alveolar cells with foamy cytoplasm were larger and more numerous, in some areas filling the alveolar spaces. Needle biopsy specimens were obtained from the lung of one patient in the sixth week of the disease and sections were taken at necropsy from the lung of the patient who died. These revealed pulmonary tissue with several spicules of irregular foreign body embedded in it. There was a fibroblastic reaction of the interstitial tissue of the lung. There were many large cells with foamy cytoplasm in the alveolar spaces. The foreign bodies were microscopically

similar to bagasse, and under the polarizing microscope these "spicules" were seen to rotate the planes of polarized light. A resume of these 11 cases may be seen in tables 3, 4, and 5.

Hunter and Perry (8) reviewed the cases that occurred in England, and concluded that out of 21 men employed in the shredder in a period of fifteen months, 10 (47.5 per cent) developed the disease. The onset of symptoms usually occurred after the men had been working on the machine for eight weeks. The disease manifested itself as an acute febrile illness with extreme dyspnea, cough with scanty, black, stringy sputum, and occasional hemoptysis. Signs were scattered throughout both lungs, and roentgenograms of the chest showed miliary shadows throughout both lung fields. They concluded that the appearances were therefore those of an acute bronchiolitis. The densities gradually disappeared over a period of six weeks, at which time the roentgenograms showed the lung fields to be clear.

TABLE 3

*History of symptoms in 11 cases of bagassosis (Sodeman and Pullen)*

CASE NUMBER	AGE	RACE	LENGTH OF EXPOSURE	COUGH	DYSPNEA	SPUTUM	HEMOPTYSIS	NIGHT SWEATS
			<i>weeks</i>					
1	18	W	4	+	+	+	+	0
2	46	W	3	+	+	+	0	+
3	26	W	20	+	+	0	0	+
4	30	N	6	+	+	+	0	-
5	34	N	—	+	+	+	0	-
6	19	W	28	+	+	+	0	-
7	27	N	104	+	+	0	0	+
8	28	N	12	+	+	+	+	+
9	27	W	—	+	+	+	+	+
10	22	W	—	+	+	+	0	+
11	20	N	16	+	+	+	+	+

#### ETIOLOGY

The exact etiology of bagasse disease still remains obscure. Sodeman and Pullen (6, 7), have demonstrated bagasse particles in the alveoli (lung biopsy and section of lung in necropsy) in patients with this disease. One may conclude that bagasse may enter the alveoli and initiate a fibroblastic reaction, and that, by digestion or absorption through the activity of cellular response, these changes are removed and a normal functioning lung (normal on roentgenologic examination) remains.

In their first report, Jamison and Hopkins isolated a fungus but did not state its characteristics or type. Castleden and Hamilton-Peterson, as well as Gillison and Taylor, failed to isolate a fungus. Where fungi were isolated, they were thought to be contaminants which were not associated with the disease.

A disease known as maple bark disease (9) presents a similar roentgenologic picture. The implication of fungi in pulmonary allergy and infection is well



A. LINK KOVEN

recognized. Asthma, caused by wheat rust (*Puccinia graminis*), occurs among grain handlers (10), as well as asthma produced by dust or grain infected with

TABLE 4  
Physical signs in bagassosis (Sodeman and Pullen)

CASE NUMBER	CHILLS AND FEVER	LOSS OF WEIGHT	PHARYNGEAL IRRITATION	DEVIATION OF SYMPTOMS BEFORE ADMISSION	CYANOSIS	EXAMINATION OF CHEST
1	0	lbs. 26	0	1	0	Diminished breath and voice sounds over base of left lung; with limited expansion; no râles.
2	+	10	0	1	0	Râles in bases of both lungs anteriorly and posteriorly.
3	+	17	0	4	0	Impaired resonance and breath sounds in base of right lung; bilateral basal râles.
4	-	-	+	3	0	Impaired resonance and diminished breath sounds in base of both lungs posteriorly.
5	+	15	0	5	0	Impaired resonance upper lobe of right lung anteriorly; no râles.
6	-	20	0	12	0	Fine crackling râles at base of left lung posteriorly.
7	+	5	+	3	0	Fine râles in base of right lung posteriorly and in right axilla.
8	+	-	-	3	0	Râles in upper half of right side of chest; vocal fremitus increased.
9	+	+(?)	-	5	+	Diminished expansion at bases of both lungs; râles throughout both lungs, most marked in bases.
10	+	+(?)	-	3	0	Fine râles bilaterally throughout pulmonary field.
11	+	-	+	2	-	Diminished expansion at bases of both lungs; coarse râles at base of right lung posteriorly.

mites. Moreover, asthma caused by *Penicillium glaucum* and *Aspergillus fumigatus* has been described by Storm van Leeuwen (11). Flood (8) reported

positive skin reactions to common air-borne fungi in patients. In 1928, Hansen (12) reported a number of cases in which asthma could be produced by spores of molds which were cultivated from the environment. The patients whom he studied also gave skin reactions to extracts of the fungi. The species to which

TABLE 5  
*Roentgenologic findings in bagassosis (Sodeman and Pullen)*

CASE NUMBER	ROENTGENOLOGIC PICTURE OF CHEST	DAYS IN HOSPITAL	FOLLOW-UP
1	Miliary ground glass mottling throughout both pulmonary fields radiating from hili, apices clear.	84	Chest roentgenologically clear one month after discharge.
2	As above.	93	Chest roentgenologically clear eleven weeks after discharge.
3	As above.	23	No follow-up.
4	As above.	31	Chest roentgenologically clear thirteen weeks after discharge.
5	As above.	9	Chest roentgenologically clear thirteen weeks after discharge.
6	As above.	19	Chest roentgenologically slightly cleared on discharge; no follow-up.
7	As above.	18	No follow-up.
8	Apices also involved.	15	No follow-up.
9	Miliary ground glass mottling throughout both pulmonary fields indicating from hili, apices clear.	86	Chest roentgenologically clear two and one-half months after discharge.
10	As above.	14	No follow-up.
11	As above.	29	Chest roentgenologically clear one month after discharge.

Hansen found the patients reacted were *Aspergillus fumigatus*, *Aspergillus glaucus* or *Penicillium glaucum*. Hopkins *et al.* (13) reported asthma resulting from the fungus *Alternaria*. H. S. Bernton (14) reported a case of asthma caused by *Aspergillus fumigatus*, which is a regular inhabitant of the soil and may be found in a dirt-contaminated environment. Fawcitt (14) summarizes

the mycotic infections that may appear in the lungs of agricultural workers as follows:

- “1. Hay-workers—infected by *Aspergillus*, *Penicillium*, and *Mucor* species, mixed.
2. Grain-workers—Infected by *Penicillium* sp. or mixed, with *penicillium* predominating.
3. Stablemen and gardeners—*Mucor* species.
4. Horsemen—*Absidia corymbifera* (one case).
5. Cattlemen—A. *Monilia* group  
B. *Actinomyces*
6. ‘*Botrytis* predominating’ in a mixed infection in a woman living next door to a stable.”

Thus the possibility that bagasse disease may be caused by a fungus has a precedent in other diseases. However, there is no clear evidence to support a relationship of a fungus to bagasse disease. It is of interest to point out that workers exposed to dust of the insulation board after processing have not as yet been reported to acquire bagasse disease. Processing which includes heat treatment (200°C.) destroys not only fungi and bacteria but allergenic protein as well.

A similarity exists between bagasse disease and an acute illness among workers using low-grade stained cotton. The latter disease presents a picture of an acute illness that develops among workers exposed to high concentrations of cotton dust (mattress makers, cotton mill workers, upholstering plant workers) and is found to be caused by inhalation of gram-negative rod-shaped bacterium (*Aerobacter cloacae*) which is contained in dust from stained cotton. This disease resembles mill fever, Monday fever, gin fever, grain fever, hemp fever, and heckling fever.

However, the clinical picture of this disease is different from that of bagasse disease. The onset is sudden (within a few hours after exposure) and lasts only one to two days. Predominating symptoms are dry throat, aches, fatigue, headache, cough, chills, fever, and nausea and vomiting.

Castleden and Hamilton-Paterson were the first investigators to suspect an allergic reaction as the cause of bagasse disease. They prepared four types of extracts: 0.1 N solution of NaOH, 0.1 N HCl, isotonic sodium chloride and 30 per cent alcohol in distilled water. Tricresol 0.25 per cent, was added to each type of extract. The extracts containing acid or alkali were neutralized before use. In one of their cases, the alkaline, acidic, and alcoholic extracts, given intracutaneously in doses of 0.2 cc., all elicited a wheal which was maximal in thirty minutes, and a flare which was maximal in thirty-six hours. The saline extract gave a flare but no wheal. Three patients tested gave positive reactions and a group of controls who did not have bagasse disease failed to react to the saline extract and were not tested with the other extracts. Hence, these investigators concluded that bagasse contains an antigen soluble in isotonic solution of sodium chloride to which workers inhaling the dust can be sensitized. They further suggest that the acute phase of the disease is possibly an allergic response to the antigen with, or more likely without, an infective element.

Sodeman and Pullen (7) repeated this work in 3 patients and 5 controls. They found positive results in each instance and concluded that the reactions

were irritation phenomena, with the release of histamine, and did not necessarily indicate sensitization to bagasse. However, the possibility that bagasse disease may be an allergic pulmonary disease is still not excluded. The syndrome described by Loeffler in 1931 of a transient pulmonary infiltration accompanied by eosinophilia in the blood, which disappears spontaneously, resembles bagassosis. However, there are differences in Loeffler's syndrome which are at variance with bagassosis such as: attacks of asthma with cough, eosinophilia and elevated sedimentation rate, paucity of râles over the involved pulmonary areas, and roentgen findings of areas of consolidation appearing and disappearing rapidly with complete clearing in a week.

Tuberculosis has been excluded by the absence of tubercle bacilli and the negative results of tuberculin tests. Hence, one must conclude that bagassosis is a pneumoconiosis due to bagasse dust (using the term *pneumoconiosis* in its general meaning, all pulmonary diseases due to dusts, whether or not fibrosis is incurred). Whether bagassosis is caused by fungi, bacteria or a series of organisms associated with the dust, or by an allergy to the bagasse or its possible bacterial contaminants or their products, or by some chemical or physical property of the dust or any combination of the above, is still open for investigation. As Hunter and Perry (8) point out, bagassosis is an industrial disease with serious complications, as evidenced by the fact that of 24 cases there were 2 deaths, a case fatality rate of 8.3 per cent.

In view of the obscurity which surrounds the etiology of bagassosis and the lack of any specific treatment, chief reliance at present lies in prevention of a dusty environment by the use of proper exhaust ventilation, water spray, or a wet method for collecting and breaking of the bales.

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# VETERANS ADMINISTRATION TUBERCULOSIS DIVISION 1945-1947<sup>1,2</sup>

## Progress Report

JOHN B. BARNWELL<sup>3</sup>

### PROBLEM

In September, 1945, immediately after the end of World War II, the Veterans Administration had at its disposal slightly more than 9,000 tuberculosis beds, of which nearly one-half were occupied by veterans of World War I. It was clear that a great many more beds would be required, for 12,000,000 troops were to become veterans and were thus to become our responsibility rather than that of the Army and Navy. It was realized that each million veterans had its quota of tuberculosis. The exact size of that quota, however, and the speed with which beds should be provided, were very far from clear. For a number of reasons, we could place little reliance upon statistics obtained from World War I. The preliminary roentgenologic screening which troops of the recent war underwent at the time of their induction would tend to make World War I statistics unduly high. Conversely, the roentgenologic examinations conducted on discharge would reveal a peak load in the immediate future rather than a gradual accumulation discovered over a period of four years, as occurred after World War I. Furthermore, we would be dealing with a group which had been subjected to a much more prolonged period of physical strain than had been the case with veterans of World War I and, in the case of our troops of occupation, with a group which had experienced intimate contact with heavily infected civilian populations in many countries. An additional element, which upset even such hypothetical calculation as we were able to make in the fall of 1945, was imposed by the very rapid demobilization which was forced upon the Services by public sentiment. This demobilization was so rapid that veterans, complete with "ruptured ducks," were for some time being created at the rate of 1,000,000 a month. In this rapid demobilization, large numbers of Army and Navy medical corps personnel were being discharged. Hence, it became necessary that hospitalized tuberculous patients be transferred promptly to our hospitals or, as was done in four instances, that we should assume the administration of entire military hospitals.

The same difficulty which applied to our estimating the number of beds which would be required applied equally to estimates of the numbers of professional and nonprofessional staff which we should recruit. The size of the one would

<sup>1</sup> Amplification of a speech delivered before the Mississippi Valley Conference in Chicago, Illinois, September 9, 1947.

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our staff of tuberculosis specialists in Veterans Administration hospitals from 202 to 395 full-time physicians and from 3 to 124 part-time physicians. We have also, although but temporarily, 180 doctors on assignment from the Army and Navy and 12 residents in tuberculosis. The number of nurses on duty has increased from 656 to 1,041 and we have, in addition, 60 cadet nurses. More than 100 cadet nurses have completed four to six months' special training in our tuberculosis hospitals.

#### PROGRESS, ADMINISTRATIVE

So much for figures. They show readily enough that the size of the job and the equipment for handling it have approximately doubled in the past two years. It is by no means so easy to satisfy ourselves or to show mathematically that there has been a similar qualitative improvement in the care of patients or, indeed, that any such improvement has occurred. Several administrative changes were introduced, however, which *should* have effected such an improvement. I should like to list them.

*Creation of Division of Medicine and Surgery:* Public Law 293 was passed by the Seventy-ninth Congress and approved by the President on January 3, 1946. This law removed the professional staff of the Veterans Administration from the jurisdiction of the Civil Service Commission, although the retirement benefits of Civil Service were maintained. Moreover, the new law permitted salaries to be fixed on the basis of professional experience and competence rather than on the basis of administrative position. Thus, a hospital manager is no longer entitled to a higher salary than a clinical director or a chief of service, and the financial inducement to abandon clinical work has disappeared in consequence. As a further encouragement to professional competence, this law granted an automatic 25 per cent salary increase to holders of certificates from the various specialty boards and set a maximum annual salary of \$11,000, subject to income taxes.

*Creation of Branch Office and Section Chiefs:* The administrative problems of the Veterans Administration are so spectacularly large, not only in medicine, but, perhaps, even more in the fields of insurance and education, that it seemed impossible to manage them from any single office. The Administrator consequently divided the United States into 13 geographical units, very much like the corps areas or service commands of the military, and established a Branch Office in each of them. Any Veterans Administration Office can be readily identified by the presence on its walls of the gaudy maps with many-colored pins which identify these branches and the various units within them. A Branch Medical Director is responsible for the medical activities in each Branch area and within his Division of Professional Services there is, amongst others, a part-time or full-time section chief for tuberculosis and a full-time assistant section chief. The following individuals have been appointed to these positions and have served, with little change in personnel, for the two years covered by this report.

<i>Branch</i>	<i>Chief</i>	<i>Assistant Chief</i>
1. Boston, Mass.	Dr. Donald S. King	Dr. George C. Wilson
2. New York, N. Y.	Dr. Gilberto S. Pesquera	Dr. Cameron St. C. Guild
3. Philadelphia, Pa.	Dr. C. Howard Marcy	Dr. Henry A. Gorman
4. Richmond, Va.	Dr. Dean B. Cole	Dr. Edgar C. Harper
5. Atlanta, Ga.	Dr. W. Atmar Smith	Dr. John F. Busch
6. Columbus, Ohio	Dr. John W. Towey	Dr. Stephen K. Molnar
7. Chicago, Ill.	Dr. Frank L. Jennings	Dr. Andrew G. Goesl
8. St. Paul, Minn.	Dr. Everett K. Geer	Dr. Russell H. Frost
9. St. Louis, Mo.	Dr. Herbert L. Mantz	Dr. Samuel S. Romendick
10. Dallas, Tex.	Dr. Julius L. Wilson	Dr. Thaddeus M. Koppa
11. Seattle, Wash.	Dr. Grover C. Bellinger	Vacant
12. San Francisco, Cal.	Dr. Chesley Bush	Vacant
13. Denver, Colo.	Dr. H. Dumont Clark	Dr. Glen Doolen

The function of Central Office is the development of policies and the supervision of their execution. Branch offices are the operating units and the section chiefs, with their assistants, are responsible to the Branch Medical Director, and so to Central Office, for the care of tuberculous veterans in all the hospitals within the area. This is a large responsibility, extending into the fields of hospital planning, staff appointments and education, and inspection. The efficiency of the several branches varies directly with the ability of their section chiefs and the time at their disposal. Our progress in this decentralization program has been slow, but in it lies our only salvation. If we can keep the personnel within the branch offices at their present level of attainment, and can maintain the interest which they have displayed at considerable self-sacrifice, the successful professional administration of our program is assured.

*Irregular Discharges:* The fact that veterans may leave our hospitals without permission or against medical advice has long been a source of difficulty with the Veterans Administration treatment program. A veteran cannot be legally compelled to stay in a hospital which he wishes to leave, nor can he be prevented, after a certain interval, from reëntering the same or another Veterans Administration hospital. This situation has encouraged the development of a certain class of "floaters" who move to our hospitals in the West or South for the winter and may return to the Adirondacks for the summer. Some of these discharges are undoubtedly a consequence of inadequacies in our service, some result from the psychological make-up of the veterans involved. We are attempting to investigate the latter factor by a social study of all veterans who left our hospitals in irregular fashion during the month of July, 1947.

A law which was designed, in some part, to counteract this tendency was approved by the President on August 8, 1946. Its primary purpose was to abolish the distinction which had previously existed between veterans with and without dependents so that those *without* dependents had been deprived of all compensation except spending money during hospitalization. The new law also provided that veterans without dependents would receive full compensation for the first six months of hospitalization. After that period, however, a major portion of the compensation would be impounded and would be returned to the patient



only at the time he received a regular discharge. If he were irregularly discharged, the impounded moneys would be retained for an additional six months. One branch medical director felt that this law encouraged veterans to leave before their first six months of hospitalization had been completed. No other medical director has expressed dissatisfaction with the working of the law although one branch office in the South found it to be disliked by those veterans with "unapproved" dependents.

This new regulation may assist in reducing the frequency of a type of discharge which is admittedly a reflection on Veterans Administration care, particularly in its psychological aspects. I would like to illustrate the difficulty of using statistics to measure any degree of improvement which we may make in this direction. In June, 1947, irregular discharges in our tuberculosis hospitals ranged from 16.4 per cent to 54.6 per cent, with a mean of 30.5 per cent. The latter value, incidentally, is comparable to the mean for irregular discharges from civilian institutions. I have recently visited the hospital with the best records and I can assure you that it is a very beautiful and comfortable place to live. It is not a really good tuberculosis hospital, however, although its staff is conducting an outstanding streptomycin and surgical program. On the other hand, the hospital with the apparently disgraceful rate of 54.8 per cent was recently opened and there is reason to believe that the neighboring institutions followed an old army custom by transferring their least coöperative patients to it on its opening day. It is encouraging, I believe, that, with the single exception of our most isolated hospital, no other unit had a rate exceeding 35.6 per cent for the month in question. As another example of the incomplete picture provided by the statistics, I would like to mention the case of a new manager who went into one of our hospitals that had held a poor reputation for years. He instituted bed-rest and discipline. With the aid of the local service organizations, the local police and taxicab companies, and indeed, the whole community and its hospital, he got rid of drunkenness and his patients for the first time were "taking the cure." I asked him to let me quote the new figures. He told me they looked worse than the old, for he had been compelled to discharge those who would not take treatment. I know the manager and I know the chief of medicine and they both tell me they now have a hospital instead of a combined "flop house and country club." I believe they have effected a real improvement, which is not evident from the statistics except for the fact that, where previously 40 per cent of the patients refused surgery year after year, such refusal is now rare.

A similar problem was handled in like manner by a new chief of tuberculosis in another of our hospitals. It developed that 10 of the 180 patients were unwilling to admit that they were in a hospital rather than a boarding house. They left amicably enough with the understanding that, if they ever wished real hospital care, they would be readmitted without prejudice.

These patients, who are unwilling to accede to the hospital regulations which we believe essential for their proper treatment, constitute only a part of our irregular discharges, but they constitute a very definite group and I am unwilling

to admit that the Veterans Administration should do nothing about them. They must receive care. We are considering the establishment of a so-called "health resort" for them, where they can live in the manner to which they have become accustomed. I have recently visited two hospitals which could be converted to such a resort and I am still looking for the personnel who could manage it.

*Compensation after Discharge:* Another administrative action which will, I believe, improve the long range results of our treatment was accomplished by a change of instructions issued by the Veterans Administration Rating Schedule Board on July 14, 1947. Previous to this change, full compensation could only be provided to a veteran for six months after his discharge from a hospital as an arrested case. At present, this compensation may be extended for two years, providing only that a tuberculosis specialist employed by the Veterans Administration certify, at intervals of six months, that the patient is not yet ready for full-time gainful employment and that he is on a program of rehabilitation with restricted activity.

*Follow-up after Discharge:* In January, 1946, we urged upon the branch offices, and upon the more numerous regional offices under their jurisdiction, the importance of following the progress of patients after their discharge from hospital by arranging for physical examinations at three month intervals. The Veterans Administration is in a peculiarly favorable position to make an attempt of this sort, for the addresses of all veterans are on file and, so long as the veterans are receiving compensation, these addresses are sure to be accurate. The attempt was made prematurely in the sense that our decentralization program was incomplete and, in consequence, neither branch nor regional offices were fully staffed or familiar with their responsibilities. As our organization improved, however, the program began to show results and it is now moderately successful. The degree of success varies considerably from office to office, depending upon the energy and ability of its staff.

*Case Finding Program:* In the very real sense that the early detection of tuberculosis facilitates its successful treatment, our adoption of the mass roentgenologic survey method should improve the quality of our care. Routine chest roentgenograms are now made on all patients at the time of their admission to all hospitals and on all veterans who visit our outpatient departments for pension or compensation examinations, unless they have been examined within the previous six months. In addition to this, annual roentgenograms are to be obtained for all hospital employees and all patients who are hospitalized for more than one year. This program is not yet completely in effect but, when it is fully established, we estimate the number examined will approximate 1,800,000 annually. In addition to our regular roentgenologic equipment, 20 photoroentgen units have been installed, and both public health departments and tuberculosis associations are helping us reduce the backlog of employees and chronic patients who are awaiting examination. During 1946, tuberculosis was diagnosed in 75 of our employees. The incidence was lower in our tuberculosis hospitals than in our general hospitals, but this ratio may not be maintained once the backlog has been eliminated and the surveys become current.

*Case Registers:* A register has been prepared in Central Office which contains the names, addresses, and what is essentially a clinical abstract, of the 35,000 veterans of World War II who have been discharged from the Services with a diagnosis of tuberculosis since 1942. Concurrently, a separate register has been prepared containing similar data for the 22,000 veterans of World War II who are receiving compensation for disability caused by tuberculosis. The data contained in these registers have never been available to the Veterans Administration before and we expect to derive great profit from them. At last we shall be able to prophesy our future case load by processes of reason rather than "by guess and by God." As copies of these registers are distributed to the branch and regional offices, and as these offices supply the data to keep their information current, we shall be able to adjudge the effects of treatment, to observe the course of disease, and to determine the advisability and effectiveness of our medical and social service follow-up.

*Liaison With Health Departments:* With the design of improving the supervision of our patients after they leave hospital, as well as in the interest of medical statistics, we have extended our liaison with public health departments. At the time a diagnosis is established, and again at the time the patient is discharged from hospital, the case is reported to both state and county or municipal departments in the patient's place of hospitalization and in his place of residence.

*Rehabilitation:* I am convinced of the value of rehabilitating veterans while they are still patients in our hospitals. Although I cannot quote figures to prove the point, it is surely true that even a very expensive program would be worth while, not only in improved morale, but also in dollars and cents, by accelerating the patients' return to gainful employment. By the term "rehabilitation" I mean to include physical medicine, vocational training, and vocational guidance; all facets of a single subject and with a single object. We have expanded the rehabilitation program considerably. It is already well established in 6 of our 19 tuberculosis hospitals. We must expand it more, and we will do so as the specially trained personnel which is required becomes available. We have commenced an interesting study in this field by setting aside an entire hospital, near Asheville, North Carolina, as a rehabilitation center, very much as the Army did in the rehabilitation of deaf or paraplegic cases. To this center come tuberculous veterans who have stable lesions and who have progressed sufficiently to be out of bed for five hours a day. They may remain there until they are able to indulge in vocational and recreational activities for as much as ten to twelve hours a day. The center has only been in operation for three months but the plan seems to be working well. It should be successful, for the idea behind it is sound. I do not believe that such a rehabilitation program will prolong the total period of hospitalization. A suggestive indication that the patients like the idea may be seen from the fact that the center has had but 11 per cent irregular discharges.

*Training of Doctors and Nurses:* As I have already mentioned, it is a shortage of doctors and nurses who are trained and experienced in tuberculosis work that is responsible for our present inability to house all tuberculous veterans in

Veterans Administration hospitals. This shortage will become worse in the immediate future when the doctors trained by the Army and Navy, and loaned to us by them, complete their terms of enlistment. It will become still worse within the next two or three years if, as we anticipate, our tuberculosis load increases by some 20 per cent. We are eager to recruit trained personnel from civilian hospitals and practice. But there is a limit beyond which we cannot go in this direction, beyond which we should not go from the point of view of the national welfare. We shall have to rely upon our own resources for much of this increase in personnel. We shall have to attract, and to train in tuberculosis work, the residents, and possibly the internes, who come into our general hospitals. I am, therefore, particularly interested in the idea of rotating our residents in internal medicine through tuberculosis units. This should be relatively simple in general hospitals containing a tuberculosis service and, as a matter of fact, it is already in effect in several instances. The system should not be impossible even in our more isolated tuberculosis hospitals.

The preparation of our hospitals for the training of nurses in the care of tuberculosis has proceeded more rapidly than was anticipated. Within a year of the establishment of the position of Nurse Specialist in Tuberculosis, we had received student affiliate nurses in 3 of our tuberculosis hospitals. One hundred cadet nurses have received this training. I am pleased to be able to say that six of seven students from Johns Hopkins returned to a Veterans Administration tuberculosis hospital upon their graduation.

Eight of our hospitals have been temporarily approved by the American Medical Association Council on Hospitals and Education for training in tuberculosis. The approval of many more is pending. The American Board of Internal Medicine now allows two years' service in an approved hospital to count as years of practice of internal medicine in qualifying for examinations.

*Centers for Thoracic Surgery:* Each of our hospitals has its group of part-time consultants, who function very much as do "visiting men" in civilian hospitals and who exercise varying degrees of responsibility, depending upon the competence of the hospital's full-time staff. The consultants have done a great deal to improve the standards of hospital care and at a cost which averages only 12 cents a patient-day. Largely through the assistance of such consultants, we have been able to increase from 5 to 40 the number of our hospitals in which such radical thoracic surgery as lobectomy and pneumonectomy can be performed. These centers must be staffed, not only with expert surgeons, but also by individuals with special training in diagnosis, anesthesia, and nursing. Before a center is certified, it must have been approved by the branch office section chief in thoracic surgery and by Dr. Brian Blades, Chief of Thoracic Surgery.

*Isolation Techniques:* Another change which we have sought to introduce into all of our tuberculosis units by administrative measures has been the introduction of isolation techniques. Our attempt has been incompletely successful, partly because of the difficulty in obtaining and installing the necessary plumbing fixtures, and in part because of incomplete acceptance by the hospital staffs of the underlying principles involved.

## PROGRESS, INVESTIGATIVE

In the two years since I joined the Veterans Administration, I have been continually and deeply impressed with the opportunities for clinical research which its facilities provide. Consider the quantity of material at our disposal in the field of tuberculosis: 15,000 patients, 80,000 veterans receiving compensation, 46,000,000 X-ray films. The Army may have had such masses of material available to it during the recent war, but only for brief periods and at a time when the main preoccupation was elsewhere. Surely such material has not been available to any other organization. From study of this material it should be possible to provide answers to many pressing questions. Moreover, at the moment we are fortunate in having an Administration and a Congress which are favorably disposed to the use of funds for research.

*Streptomycin:* Our major research efforts during the past year or more have been directed toward investigating the effects of streptomycin upon human tuberculosis. The Veterans Administration is not, and should not be, in a position to make the first clinical trial of a new drug, either in the treatment of tuberculosis or any other disease. Once a new drug has been tried, however, and has been shown to have some promise of effectiveness without undue toxicity, the Veterans Administration is peculiarly, and perhaps uniquely, fitted to conduct a large scale evaluation of its effectiveness and the best regimen for its administration. Our immense resources of clinical material, our financial resources, and the rather loose but definite control which we can exert over our many hospitals, combine to give us a great advantage over civilian investigators. We have sought to exploit these advantages in our study of streptomycin. The Bureau of the Budget placed at our disposal a million and a half dollars in the fiscal year 1947 and two million dollars in the present fiscal year of 1948. I would like to emphasize that more than 98 per cent of our expenditures has consisted of purchases of streptomycin and less than 2 per cent has been devoted to administrative purposes.

Our early difficulties were not financial, but were concerned with obtaining streptomycin. By June, 1946, the pharmaceutical industry had appreciably diminished these difficulties. In coöperation with the Army and Navy, a protocol was prepared setting forth criteria which were to be followed in the selection of cases for treatment and the dosage regimen which was to be used. Study units were established in 7 Veterans Administration hospitals during the course of the summer of 1946. One of these units was designated to study only genito-urinary tuberculosis and, to facilitate this study, suitable cases from all over the East were collected at our hospital in New York City. Similar arrangements were made for patients with tracheobronchial disease and draining cutaneous sinuses.

A most successful means of maintaining liaison between the study units has been through Streptomycin Conferences which are attended by all the investigators, by representatives of federal agencies and national societies, and by a number of consultants. These conferences have been held in St. Louis and Chicago and have been of three or four days' duration. From the decisions reached at these conferences, the progress of the investigation can be fairly well charted.

At the first conference, in December, 1946, the preliminary results were reviewed and found to be sufficiently favorable to justify enlargement of the study. The number of participating hospitals was therefore increased from 7 to 20. The second conference, held in February, 1947 put into effect a decision to decentralize the control of streptomycin to the branch offices. Streptomycin committees were established in each office and were authorized to supply streptomycin for the treatment of appropriate cases in any Veterans Administration or contract hospital within their area which was able and willing to abide by the terms of the protocols for each of the more important types of tuberculous disease. By May, 1947, at the time of the third conference, some 900 cases had completed treatment or were sufficiently near completion so that the results of the single regimen which had been employed up until this time could be evaluated. It was the decision of this conference to explore new regimens and the study units divided themselves into three groups, each of which adopted a different schedule. At the fourth and most recent conference, the effectiveness of these new regimens upon 500 additional cases was reviewed and still other schedules were adopted. The new regimens were designed to examine the effectiveness of still lower doses of streptomycin and combinations of the drug with collapse procedures and with promin.

I have been much impressed with the fact that in a coöperative investigation of this sort it is possible to collect uniform data on a large series of cases in a short period of time. In scarcely more than a year we have collected information on 1400 cases in the 20 study units alone. I think there can be no doubt but that, in the course of collecting these data, a considerable proportion of the hospital staffs were interested and lifted above themselves by virtue of their participation in an important clinical investigation. I should like to emphasize that, although the study was necessarily designed in rather an arbitrary and centralized fashion, it has been our constant attempt to place the responsibility for decision as to changes of policy upon the shoulders of the several investigators. It may now, I believe, be regarded as a coöperative venture in the best sense of the word.

*Control of Air-Borne Infection:* The decision to explore the efficacy of germicidal lamps upon the transmission of tuberculosis in our hospitals was made at a conference with civilian authorities in February, 1947. Surveys for the complete equipment of two typical hospitals have been made. When the installations are completed, it will be a matter of great interest to observe the incidence of new disease in these hospitals in comparison with hospitals not so equipped. The expense of the equipment, as well as a certain skepticism of its effectiveness, has made it desirable to start the study in a rather limited way. The oil treatment of blankets, bed linen and floors has been adopted by one unit in the manner suggested by the office of the Surgeon General of the Army.

*BCG Vaccination:* It has been decided to delay any study in this field until results of the large scale investigation initiated by the U. S. Public Health Service become available.

*Emotions in Tuberculosis:* A committee under the joint chairmanship of Dr. Carl Binger of New York and Dr. James Waring of Denver has been formed to investigate this subject. The team operating under the guidance of the com-

mittee is to be composed of a psychiatrist, an internist, a social worker and a psychiatric social worker, all of whom have had experience in tuberculosis. They will start at Sunmount, New York and spend two to four months in each tuberculosis hospital. The personnel for this undertaking is now being sought. *X-ray Film Depository:* The Army and Navy have turned over to the Veterans Administration all the induction and separation films on ex-service men and women. This collection, composed of 46,000,000 films, is the largest file ever made and is in a single warehouse in Washington. Seventy-five per cent of the films have already been catalogued and are available for study; the process is continuing at the rate of 31,000 a day. The collection should be an invaluable focus for the study of a variety of problems. Certain films may be loaned to Veterans Administration and contract hospitals to assist in the treatment of hospitalized veterans. We have already used some of these films to make a spot check of the compensation rolls of two regional offices. From these samples, we have reason to suspect that a number of cases should never have received compensation and that some should never have been diagnosed as tuberculosis. The number of such errors alone appears sufficiently large to justify the financial outlay involved in preserving the depository; in fact, a careful study of the material should result in saving the Government enormous sums of money.

#### SUMMARY

I have attempted to describe the events which have transpired in the tuberculosis service during the last two years. I have undertaken this report with some reluctance for, although all the steps which have been made have obviously been designed to improve the medical care of the tuberculous veteran, it is difficult to describe their effectiveness with any precision. It is easy enough to prove that the patient load and the size of our staff has doubled. It is much less easy to prove that the quality of care, our chief concern, has improved in similar fashion. The difficulty arises in part from the usual difficulty in attempting to quantitate a qualitative change, and in part from the decentralization program. The latter move, necessary as it was, leaves Central Office in considerable ignorance as to what is going on in the hospitals. In the long run, the quality of patient care will vary directly with the quality of the staff, their professional competence, their diligence, their interest, and their enthusiasm. Our chief objective, therefore, must be the training and recruitment of good physicians and nurses. We have a good deal to offer them. They have everything to offer us.

I have recently returned from a trip in which I visited 11 tuberculosis units from Kentucky to California. Some were Dean's Committee hospitals in large metropolitan areas, some were unsponsored hospitals in isolated areas from the Black Hills of the Dakotas to the deserts of the Southwest. I observed a genuine desire on the part of a majority of the staff to do a better job. There seemed to be a general belief that improvement had been accomplished in the past two years and a very healthy realization that there was room for further improvement. Of the 11 hospitals which I saw on this occasion, I was able to commend 5 and to tolerate 3; the remaining 3 appeared unsatisfactory. The major source of my

dissatisfaction was that Chiefs of Service were not sufficiently familiar with the cases on their wards. Sometimes the lack of familiarity originated in that old governmental bugaboo, paperwork. Sometimes, and most unexpectedly to me, it seemed to arise from a preoccupation with the patients who were receiving streptomycin. Thus, not only did the patients outside this group fail to receive streptomycin, but they also failed to receive adequate supervision in other directions. I do not know whether this group of hospitals is representative of the entire group. Certainly we visited some very isolated places. Isolation itself, however, was not the deciding factor. One isolated hospital was doing a nearly perfect job and one of the Dean's Committee hospitals appeared to have slipped backward.

On the whole, I returned heartened. The important thing I learned was that the veteran himself is not an insuperable obstacle to good tuberculosis treatment in our hospitals. If good treatment can be provided in a few hospitals, it can be provided in all, and there are now large numbers of us who are determined that it will be provided.

#### SUMARIO

#### *División of Tuberculosis, Administración de Veteranos, 1945-47; Repaso de Sus Obras*

He tratado de describir los desenvolvimientos observados en el servicio de lucha antituberculosa durante los dos últimos años. Empecé esta tarea con alguna vacilación, pues aunque todo lo hecho tenía manifiestamente por fin mejorar la asistencia médica del veterano tuberculoso, es difícil exponer la efectividad de lo realizado con la menor certidumbre. Por demás fácil es demostrar que el número de enfermos ha doblado a la par que el tamaño del personal técnico, pero resulta mucho menos fácil demostrar que ha mejorado en forma semejante la calidad de la asistencia, que constituye nuestra principal misión. La dificultad proviene en parte de lo difícil que es acuantiar una alteración cualitativa, y en parte del nuevo plan de descentralización, que, necesario como es, deja a la Oficina Central bastante a oscuras de lo que sucede en los hospitales. A la larga, la calidad de la asistencia variará en razón directa a la calidad del personal técnico, con su competencia profesional, diligencia, interés y entusiasmo. Nuestro principal objetivo debe consistir, pues, en la preparación y obtención de buenos médicos y enfermeras. Mucho tenemos que ofrecerles y ellos nos pueden ofrecer todo.

He regresado hace poco de un viaje en el cual visité 11 unidades antituberculosas desde Kentucky a California. Algunas representaban hospitales regentados por Comisiones de Decanos en grandes zonas metropolitanas, y algunos hospitales sin patronos en zonas aisladas desde las Montañas Negras de las Dakotas a los desiertos del Sudoeste. En todas partes observé verdadero afán de parte de la mayoría del personal técnico por hacer mejor trabajo; impresión de que se había logrado mejoramiento en los últimos dos años, pero comprensión muy juiciosa de que cabía aun obtener más mejora. De los 11 hospitales que vi



en dicha ocasión, pude elogiar 5 y tolerar 3; los otros 3 parecían inadecuados. La causa mayor de mi descontento procedió de que los Jefes de Servicio no estaban suficientemente al tanto de los casos en sus salas; a veces ese desconocimiento partía del viejo coco gubernamental: papelería; a veces, y para mi, algo inesperadamente, del enfrascamiento en el grupo de enfermos que recibían estreptomina, de modo que los demás pacientes, no sólo no recibían estreptomina, sino que tampoco recibían vigilancia adecuada en otros sentidos. No sé si este grupo de hospitales representa todo el grupo. No cabe duda de que nos metimos en algunos sitios muy aislados, pero el aislamiento no era de por sí el factor decisivo. Un hospital aislado realizaba una obra casi perfecta y uno de los hospitales regentado por una comisión nombrada por el Decano de la Facultad de Medicina parecía haber perdido terreno.

En conjunto, regresé alentado. Lo que aprendí de importancia es que el veterano mismo no constituye un obstáculo insuperable al buen tratamiento antituberculoso en nuestros hospitales. Si pueden ofrecer buen tratamiento algunos hospitales, lo pueden ofrecer todos, y somos muy numerosos los determinados hoy día a que se ofrezca ese tratamiento.

# A COMPLETE COMMUNITY SURVEY FOR TUBERCULOSIS<sup>1</sup>

A Second Report on Effectiveness of the Procedure as a Method of Tuberculosis Control

ROBERTS DAVIES,<sup>2</sup> G. A. HEDBERG<sup>3</sup> AND MARIO FISCHER<sup>4</sup>

## INTRODUCTION

In 1946, one of the writers reported a study dealing with the incidence of new cases of tuberculosis in a small rural area, after a complete community survey for tuberculosis with hospitalization of all active cases (1, 3). That survey was followed by a sharp drop in the incidence of new cases. It was concluded that a complete community survey for tuberculosis is probably a practical and effective method of tuberculosis control. Moreover, as the occurrence of new cases stopped so promptly after the survey, it was further concluded that most cases of clinical tuberculosis in the community studied had probably been the result of recent exogenous infection. Because of the important practical and theoretical implications of these conclusions, it seemed advisable to test the method in a larger community. As in 1943 a similar complete community examination of the village of Ely, Minnesota, and the surrounding rural area, had been conducted by the writers, it was decided to conduct a second study of the same area in the fall of 1946 in an effort to check the effectiveness of the first survey.

## COMPOSITION OF COMMUNITY

Ely, a village of approximately 6,000 people on the edge of the northern wilderness of St. Louis county, is built around two underground iron mines. The tourist trade and logging industry are also important to the economy of the town. The commercial and social life of the surrounding rural area and the lake and forest country is centered on the town, as there is no other shopping center close by. The area has a rather large foreign-born population, chiefly Finns and Yugoslavs, with some Scandinavians and Italians.

## SURVEY METHOD

The details of the survey method and the costs entailed have been outlined in previous publications (2, 4). In the first survey, beginning in September 1943, the victory aides, who constituted a part of the local civilian defense organization, made a house-to-house canvass of the whole area, rural as well as urban. A record was made for each individual, giving name, age, sex, marital status, address, occupation, date and place of birth, name and relationship of nearest relative, place and date of last previous chest film, and name and address of the family physician. The importance of the survey, as well as its methods, were explained in each house. All households were later notified when to expect the

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mobile X-ray unit in their area. Persons who did not come in for examination when expected were called by telephone or visited again by one of the volunteer workers or by the public health nurse attached to the Unit.

As at the time of the 1943 survey the two mining companies in the town were about to begin a compulsory roentgenologic study of all their personnel, it was agreed that, while mining company employees would not be denied examination, no effort would be made to include them in the mobile unit survey.

The mobile X-ray unit examination consisted of single 4 x 5 inch films. All films were interpreted by one of the writers. The mining company employees each had a single 14 x 17 inch film which was read by roentgenologists elsewhere. The mining companies reported the number of persons examined and the number of persons diagnosed as having probably inactive pulmonary tuberculosis of the adult type. Only those persons who were thought to have active tuberculous lesions were reported by name and address.

The family physician was sent a brief report of the roentgenologic findings of every person examined. In the case of persons showing evidence of pulmonary disease, a letter was sent to the patient asking him to consult his physician for an interpretation of the findings, and requesting sputum specimens for which containers were supplied. Three specimens for microscopic examination and one for culture were requested in each case. A single 14 x 17 inch chest roentgenogram was also requested for each such person. These films were paid for by the sanatorium and interpreted by the investigators.

Records for all patients with lesions which were thought to represent so-called adult type tuberculosis were filed in the sanatorium outpatient department for perpetual follow-up. With two exceptions, sanatorium study was advised on all persons suspected of having active tuberculosis.

The second survey in 1946 was conducted in essentially the same way except that an effort was made to examine everyone in the community at the mobile X-ray unit and no separate survey by the mining companies was made. All films were interpreted by one of the writers. After the survey was completed, records from the two surveys were reviewed and compared case by case, and an attempt was made to resolve any apparent inconsistencies.

Some sources of error in the tabulation in table 1 should be pointed out. There was considerable competition among the volunteer canvassers to achieve a high percentage of examinations. The spirit of competition engendered a temptation not to report on the census cards those persons whom the volunteer considered likely to be uncoöperative. Therefore some persons listed under the column heading of "Not present" should properly have been in the "Persons present but not examined" column. Some spot checks make it seem likely that this "error" did occur, but apparently in only a very few instances.

In the 1943 survey, roentgenograms were made of 854 persons by the mining companies and 492 of this group were not examined by the mobile X-ray unit. Sixty-nine of these 492 people were not reexamined in 1946, although they were living in the community then. These are all tabulated among the 332 persons, "Negative for adult type tuberculosis" in 1943, and "Persons not examined" in

1946, although it is possible that some of them may have had apparently inactive tuberculosis diagnosed in 1943.

Because in a few cases the same person appeared under different names in the two surveys, it is possible that in a few instances the same individual may have been tabulated twice. In the majority of such instances, other data have been sufficient to make the identification certain.

In each instance in which the diagnosis of the 1946 survey differed from that made in 1943, the case is tabulated according to the final decision made after review of all films and other pertinent data.

A considerable change in the composition of the population occurred in the interval between the two surveys. Of the 5,964 persons in the 1943 census, 1,223 (20.5 per cent) had either died or moved away from the community before the 1946 survey. Moreover, 1,919 (32.2 per cent) new persons had been added to the community by birth, by immigration, or by the return of citizens who were absent from Ely in 1943. A major portion of the latter group were persons who had been in military service. There was a net gain of 11.7 per cent in the population.

The second survey afforded an opportunity to check the accuracy of the interpretations of both surveys. Evidence of tuberculosis was found in 114 persons who were examined in both surveys. Of these, 14 had been considered to have no tuberculosis in the first survey and were correctly diagnosed only after the 1946 film was interpreted. Another 20 of the 114 persons who showed evidence of tuberculous lesions were considered negative on the original reading of the 1946 films and were correctly classified only after comparison with the 1943 reading. The great majority of the cases overlooked showed minimal, discrete, fibroid scars, which were probably of little clinical significance. However, 4 of the 34 cases mistakenly read as negative had moderately advanced disease.

The completeness of the community screening is obviously of cardinal importance as upon it depends the relative success or failure of this method of tuberculosis control. In the first survey, 97.8 per cent of the population was examined and, in the second, 89.6 per cent. The better record of the 1943 survey came about largely because examination of all mining company employees was made compulsory at that time. Of the total of 7,883 persons living in the area during one or both surveys, only 403, or 5.1 per cent, were not examined at least once.

The 1943 census included 129 persons who, for one reason or another, were not examined in that survey. These individuals were not all included in the group "Persons present but not examined," during the second survey. Fifty-six of them were no longer living in the community in 1946; 30 were examined and showed no evidence of tuberculosis; only 42 were present in the community though not examined, while one was examined and found to have active tuberculosis. This individual did not, in fact, refuse examination in 1943, but was living in a remote cabin in the woods at that time and failed to hear of the survey until after it was finished.

Of the 695 persons living in the area in 1946 who were not examined in that

survey, 332 had had negative chest films for tuberculosis in 1943; 186 had had satisfactory chest films in 1945 or 1946; 33 were confined to their homes or to a hospital by illness; and 33 were five years old or younger.

### RESULTS

Of the 5,672 persons with chest films which were considered negative for reinfection type tuberculosis in 1943, 4,206 were reexamined in 1946 and were again found negative (table 1). No one in Ely, whose chest roentgenogram was negative for reinfection tuberculosis in 1943, has been demonstrated to have developed the disease since.

One hundred eight (72 per cent) of the 149 persons who had evidence of apparently inactive tuberculosis in 1943 were reexamined in 1946 and showed no significant change in the findings.

TABLE 1

*Persons examined, and status as to adult type tuberculosis in 1946 survey, classified by persons examined in 1943 survey, and status as to adult type tuberculosis—Ely, Minnesota*

PERSONS EXAMINED IN 1943 AND STATUS AS TO ADULT TYPE TUBERCULOSIS	TOTALS	PERSONS EXAMINED IN 1946				PERSONS NOT EXAMINED IN 1946		
		Sub-totals	Negative	Apparently inactive	Active or questionably active	Sub-totals	Present in community	Not present in community
Totals.....	7,883	5,965	5,832	127	6	1,918	695	1,223
Persons examined in 1943.....	5,835	4,320	4,206	111	3	1,515	348	1,167
Negative.....	5,672	4,206	4,206	—	—	1,466	332	1,134
Apparently inactive.....	149	108	—	108	—	41	16	25
Active or questionably active.....	14	6	—	3	3	8	—	8
Persons not examined in 1943...	2,048	1,645	1,626	16	3	403	347	56
Present in community.....	129	31	30	—	1	98	42	56
Not present in community...	1,919	1,614	1,596	16	2	305	305	—

Forty-one persons with evidence of apparently inactive tuberculosis in 1943 were not reexamined in the 1946 survey. Of this group, 15 had had recent satisfactory chest films; 11 had moved away from the community and were untraced; 9 were still living in the community, but were not reexamined (chiefly because they were uncoöperative); 4 were dead of nontuberculous disease; and 2 had "reactivated" their disease eighteen months and two years, respectively, after the original examinations. Both of these persons were admitted to the sanatorium, and one died there of tuberculosis.

The fact that 9 of the 139 persons with apparently inactive tuberculosis who remained in the community were not examined in three years is a rough measure of the adequacy of the follow-up program. Five of these 9 persons had been seen, but not examined, within the interval, and in each of these cases, the sanatorium outpatient department thought there was insufficient likelihood of active

disease to justify forcing an examination. The remaining 4 persons (3 per cent of those with apparently inactive tuberculosis remaining in the community), represent more truly the absolute deficiency of follow-up.

Fourteen persons are classified as having had active or suspiciously active tuberculosis in 1943. Eight of these persons were admitted to the sanatorium where 6 of them remain as patients. One of the remainder, an 82-year-old man, stayed at home under supervision and recovered. Another, with suspiciously active tuberculosis, died at home (apparently not from tuberculosis) before sanatorium admission could be effected. Three of this group left the county after the diagnosis was made. Of these three persons, one has not been traced, but the other 2 have been reported to the proper health officers for follow-up. Neither has been hospitalized and both are apparently still in fairly good health. One person is still classified as having questionably active disease and has not yet been admitted to the sanatorium. Examinations of the sputum of this patient have been negative.

In 3 of the 14 cases considered as active or suspiciously active tuberculosis, the present diagnosis was not made until the 1946 survey. Some honest doubt still remains as to the presence or absence of tuberculosis in 2 of these 3 cases, but the abnormal density now evident was found, on review, to have been present in 1943. The third person in this group was not examined in the mobile unit survey in 1943, but had a 14 x 17 inch film made at that time which was thought to show inactive tuberculosis. On review of that and subsequent films, it appears probable that the disease was active at that time.

In the 1946 survey, 6 persons (.09 per cent of the population), were classified as having active or suspiciously active tuberculosis. Three of these are the persons mentioned above who showed suspicious evidence of active tuberculosis in 1943, which was not then recognized as such. One, also previously mentioned, is the person who was away in a remote cabin at the time of the first survey and was not examined. This man has had cough, expectoration, and dyspnea for at least ten years and the appearance of his chest film suggests a very old lesion. The other two were both in military service during 1943. One served in the United States Navy from July, 1942, to the fall of 1945, and apparently developed clinically evident tuberculosis during that period. He had a pleural effusion in 1919. The other man developed tuberculosis while serving in the United States Army in England in December, 1943. Five of these 6 persons have been admitted to the sanatorium. In the 6th case, activity of the lesion is still considered questionable and admission has not yet been advised.

To estimate the effectiveness of the 1943 survey as a tuberculosis control measure, the number of new cases of tuberculosis which actually developed in the three year period between the two surveys has been compared with the number that might have been anticipated if no survey had been made. The only case of tuberculosis that developed in the area after the 1943 survey was that of a 46-year-old woman, previously in apparently good health, who developed tuberculous meningitis in 1945 and died after a short illness.

To estimate the number of new cases that would have been anticipated, we

searched all available records of patients from the Ely area who were admitted to the sanatorium or seen in the outpatient department since January, 1938. For each patient all available data were utilized to determine the approximate date of onset of the disease.

Of more than 200 records reviewed, only 24 could be found in which the onset could reasonably be determined to have occurred between January 1, 1938, and the beginning of the first survey in September, 1943. In most of these cases, the onset was tabulated as the date of first symptoms preceding a chest roentgenogram which showed an apparently recent lesion. Five of these cases occurred in 1938, 4 in 1939, 5 in 1940, only one in 1941, 4 in 1942, and 5 in 1943.

In order to calculate conservatively, the arithmetic average of the yearly incidence for the six year period has been taken. This average indicates an expected annual incidence of four cases. In the three year period from 1943 to 1946, therefore, 12 cases could have been expected if there had been no change in the population.

To arrive at an average population for the years 1943 to 1946, the counts of the survey census of 1943 and the survey census of 1946 have been averaged, yielding 6,312 persons as the average population for the period. It is known from other data that the population in 1938 was somewhat higher than in 1943, but no accurate figures are available. It seems very unlikely that the population dropped as much as 20 per cent in the interval, but, in order to calculate conservatively, that figure has been used. On this basis, the average population for the years 1938 to 1943 has been calculated to have been 6,750 persons.

The anticipated number of new cases of tuberculosis has been corrected for the change in population so that 11 has been used as the number of new cases that might have been expected if the survey had not been done. Unfortunately, this figure cannot be corrected for changes in the age and sex distribution of the population, but it does not seem likely that such a correction would be significantly large as the changes incident to the war were presumably operative to the same degree in both periods. If the actual incidence of one compared to an expected incidence of 11 is checked by the Chi Square method, a Chi Square value of 8.3 and a probability value of .0044 are derived. In other words, only once in 227 times could such a difference occur by chance alone.

#### DISCUSSION

This analysis, therefore, supports the conclusion of the original and much smaller study, namely, that a complete community roentgenologic survey for tuberculosis, with adequate treatment of all active cases discovered and adequate follow-up of all apparently inactive cases, is a practicable method of tuberculosis control.

It may be assumed that the success of such an anti-tuberculosis campaign is dependent on satisfying the following conditions: (1) The area treated must contain a complete and fairly separate population group. In other words, if a village is to be surveyed, any suburban or rural areas having a population that works or trades in the village should be included. (2) No large immigration of unexamined persons should occur after the survey. (3) A high percentage of the

population must be examined within a relatively short period of time. (4) All, or almost all persons found to have definite or suspicious evidence of tuberculosis must be adequately examined. (5) All or almost all of those found to have active tuberculosis must be isolated and treated, preferably in a sanatorium, until their disease is arrested. (6) All or almost all persons found to have apparently inactive adult type tuberculosis must be reexamined at regular intervals so that any reactivation of disease will be diagnosed and treated promptly.

It would not be anticipated that surveys in communities where these criteria cannot be satisfied would be an effective method of tuberculosis control. The results of this study also support a corollary of the first conclusion, namely, that, as the diagnosis and treatment of all, or almost all, the active cases of tuberculosis in this community were followed promptly by a sharp drop in the incidence of new cases, it is reasonable to assume that in this area, at least in recent years, most cases of clinical pulmonary tuberculosis have been due to recent exogenous infection. Because in most instances information is not available concerning the tuberculin sensitivity, prior to the onset of disease, of the persons who developed tuberculosis, no inferences can be made as to whether primary exogenous infection or exogenous reinfection may have been responsible.

Because only 6 persons in the community were found to have active or suspiciously active tuberculosis in the second survey, it is believed that the three year interval between the first and second surveys was a satisfactory one in this area. Such an interval might well not be optimal in a different area with a different incidence of tuberculosis and a different rate of change in the composition of the population.

It should be emphasized that the conclusions reached are based on the analysis of a very small experience and should therefore be considered as only tentative. As this small experience suggests that a practicable and very effective method of tuberculosis control is available, it would seem advisable to test the method on a larger scale in communities where the presumed requisites for success are present.

#### CONCLUSIONS

1. A complete community roentgenologic survey for tuberculosis was made in Ely, Minnesota and the surrounding rural area. This survey, which included examination of a high percentage of the population, hospitalization of patients with active disease, and adequate follow-up examination of those with apparently inactive disease, has been followed by a sharp drop in the incidence of new cases of tuberculosis. This is the second time such a result has been demonstrated.

2. In the community studied, most cases of clinical pulmonary tuberculosis, which occurred in recent years, have apparently been the result of recent exogenous infection.

#### CONCLUSIONES

*Censo Colectivo Integral de la Morbilidad Tuberculosa. Segundo Informe*

1. Un censo radiológico colectivo integral en busca de tuberculosis, con exáme-



nes de un elevado porcentaje de la población, hospitalización de los casos activos y adecuados exámenes subsiguientes de los casos aparentemente inactivos, haido, por segunda vez, seguido de una baja decidida en la incidencia de nuevos casos de tuberculosis.

2. En las colectividades estudiadas, la mayor parte de los casos de tuberculosis pulmonar clínica observados en los últimos años han sido aparentemente debidos a infección exógena reciente.

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# PATHOLOGY OF REINFECTION<sup>1</sup>

Some Sources of Diagnostic Errors

WALTER PAGEL AND C. H. C. TOUSSAINT

## INTRODUCTION

*Definition:* By reinfection is meant a tuberculous infection occurring in a person in whom a previous primary infection is anatomically healed. This enables the reinfection lesion to take the shape of a fresh primary complex; that is to say, a focus will form at the site of entry of the tubercle bacilli, followed by a homologous caseous focus in the regional lymph nodes.

Reinfection should be distinguished from *superinfection*. The latter term is used to designate a repeated infection from without in a person in whom primary infection has not completely healed anatomically and biologically.

In contrast to reinfection, superinfection may set up a fresh focus at the site of entry of the tubercle bacilli, for example, in the lung, but this will not be followed by a caseous change in the regional lymph node.

*Diagnosis:* The anatomical diagnosis of reinfection in tuberculosis is beset with pitfalls. While it was formerly regarded as extremely rare and probably too seldom diagnosed, there now seems to be a tendency to find it too often and diagnose it on insufficient evidence.

The position is quite clear in those cases in which an entirely healed primary complex (usually ossified) is found in the lungs and a fresh tuberculous lesion in a different system, *e.g.*, a tuberculous ulcer in the tonsil followed by caseation in the cervical lymph nodes. In such situations, there is a fresh lesion of the primary complex type, which is unrelated to an obsolete, typical primary complex. This contingency is occasionally observed, usually in elderly people.

The interpretation becomes much more difficult when the two sets of lesions are encountered in the same organ, notably in the lung. Even when reinfection suggests itself, because of obvious age differences between the two lesions and their situation in different parts of the organ, the diagnosis may be open to criticism. It is difficult to determine the age of tuberculous changes. Fresh caseation may occur in an actually old but recrudescient lesion. Moreover, fresh looking changes, at a distance from the now obsolete primary complex, may have originated from it at a time when it was viable. In a similar way, it is difficult to estimate the age of an obsolete lesion, although broad outlines may be accepted (1). It has been said that ossification takes many years to develop, and therefore only occurs in persons older than forty (2), but firmly ossified foci have been observed at the age of fourteen to fifteen years (4). The time needed for a primary lesion to become obsolete, and even ossified, seems to vary greatly and in some cases appears to be shorter than is commonly believed. At all events, obsolescence, including ossification, does not prevent a focus from having been the source of a fresh looking and progressive lesion.

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## OBSERVATIONS

*Apparently recent changes of endogenous origin from an obsolete lesion*

*Postmortem examination 1945: 148:* Examination at necropsy of a 23-year-old woman revealed a firmly calcified and histologically quiescent primary complex in the right lower lobe and in a lymph node at the bifurcation of the trachea. No histological evidence of reerudescence was present in any of the hilar lymph nodes. Spinal caries with a partly calcifying and partly fresh cold abscess was present, as well as an empyema. There was a cavitating infiltration in the right upper dorsal infraclavicular zone of one lung.

*Comment:* Although it is possible that the fresh infiltration in the lung could have been caused by exogenous superinfection, it is likely that the still active and progressive spinal caries, with calcifying cold abscess, was derived from a primary lesion, which also shows calcification.

*Postmortem 1944: 191:* Postmortem examination of a male, aged 6½, revealed a peppercorn-sized firmly calcified primary focus in the right upper lobe with slightly larger and also firmly calcified complementary focus in an anterior mediastinal lymph node. Histological examination failed to reveal signs of recrudesence in either focus or in any of the hilar lymph nodes. There was extensive fresh appearing caseation of the right suprarenal and a constrictive polyserositis (pericardium, peritoneum). The gastro-intestinal tract was free of abnormalities.

*Comment:* This observation shows that, even in a child, disseminated, *i.e.*, obviously hematogenous, tuberculosis may be encountered with the primary complex, even though its only possible endogenous source is firmly calcified and histologically obsolete.

*Postmortem 1945: 25:* The patient was a 54-year-old male who had had an amputation of the right arm for bone tuberculosis some years ago. Postmortem examination (1945: 25) revealed an obsolete primary complex in the right lower lobe. The other hilar lymph nodes were free from caseation on minute examination. There was bilateral symmetric spread of ulcero-fibrous focal groups with small interspersed punched-out cavities.

*Comment:* This patient had progressive bilateral symmetrical pulmonary tuberculosis of the disseminated (hematogenous) type and bone tuberculosis, although the primary complex, which was probably the original source of the lesions, was firmly calcified and obsolete.

*Postmortem 1945: 278:* The patient was a 37-year-old woman who had had her right kidney removed for tuberculosis three years ago. On postmortem examination (1945: 278), the left kidney showed fresh and extensive caseous pyonephrosis. There was a miliary spread in the bladder and a caseous ureteritis. An ossified primary complex was present in the left upper lobe.

*Postmortem 1946: 88:* A postmortem examination of a woman, aged 35, revealed an ossified primary complex in the right subapical area. A firmly calcified focus, without complementary changes in the lymph nodes, was found in the right upper lobe. There was extensive bilateral caseous tuberculosis of the kidneys.

These few cases illustrate the fallacy of the argument that obsolescence and ossification exclude a lesion as the original source of still fresh and progressive

tuberculous changes. This is true, in spite of the absence of any evidences of recrudescence in the lymph nodes, or elsewhere, which could have filled the gap between the obsolete primary and the still fresh blood-borne lesion in the periphery. The same conditions obtain equally to fresh processes that are obviously hematogenous and found outside the lungs and to pulmonary lesions whether associated with extrapulmonary tuberculosis or not.

The majority of cases of "chronic disseminated tuberculosis of the lungs" show an obsolete primary complex as their only probable source and no evidence of exacerbation therein (3).

Thus, a true primary lesion, though long extinct, may be the original source of fresh and progressing changes. Conversely, it is surprising how long the primary changes may remain soft, infectious, and devoid of calcification.

*Persistence of the "soft state" for a long time in either or both constituents of the primary complex*

*Postmortem 1947: 114:* The patient was a 23-year-old woman who had had a left-sided pleural effusion five years before death, developed Pott's disease of the thoracic spine two years later, and eventually died from tuberculous meningitis. At necropsy, no changes were found in the lungs except a small focus 0.5 cm. in diameter in the dorsal and sub-apical areas of the right upper lobe, which was situated 1.5 cm. below the pleural surface. The focus was well defined, but, with the exception of a pinpoint calcified area, was quite soft. Attached to the mediastinal aspect of this part of the lung, there was a superior tracheobronchial lymph node 3 x 2 x 1 cm., which was encapsulated and contained two pinpoint calcified areas, but was otherwise soft and caseous.

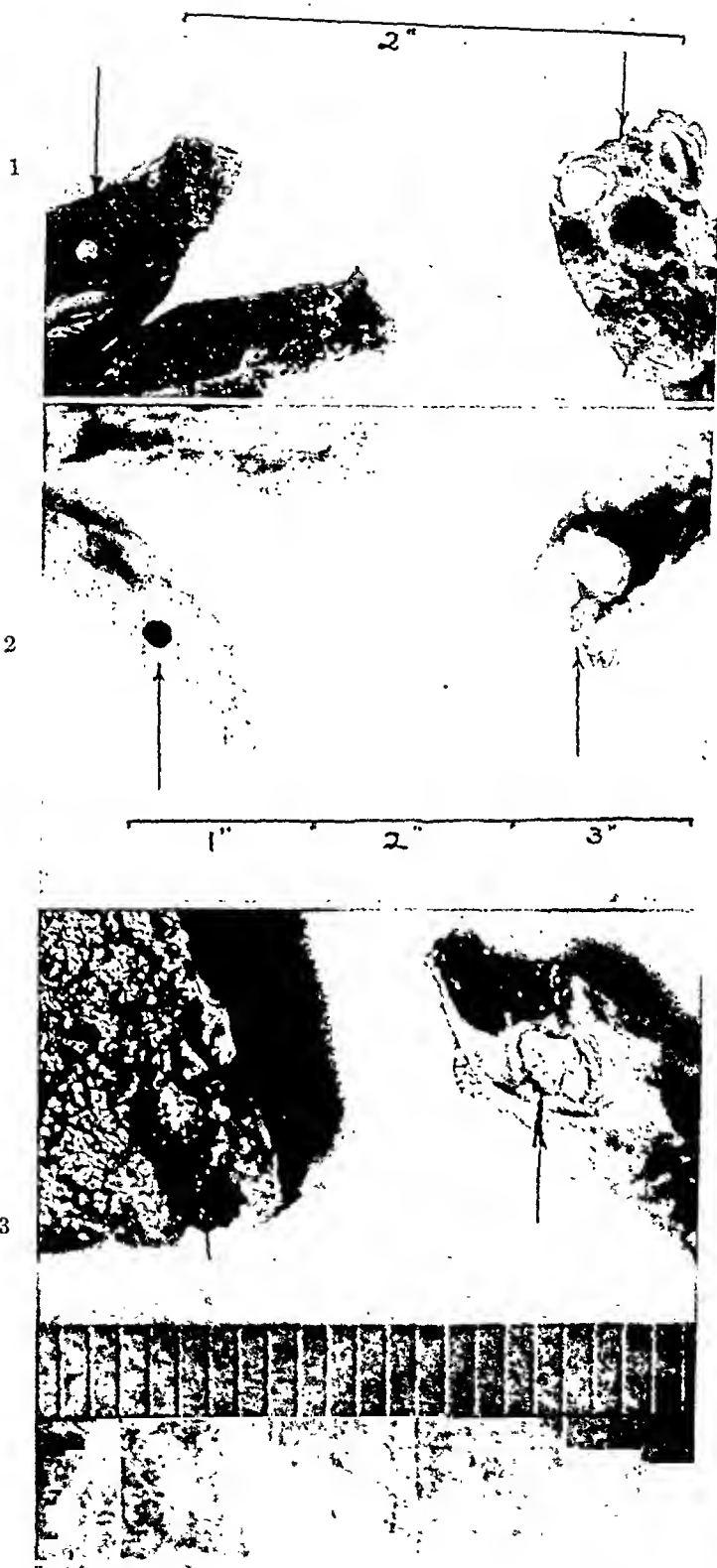
*Comment:* Five years after a pleural effusion, (obviously the first manifestation of primary tuberculosis) the primary complex found in this patient was still soft, caseous, and represented a possible source for the fatal meningitis.

It is even more common to find that *one component of the primary complex*, usually the lymphatic focus, is still soft and viable, while the other one is firmly calcified or ossified. In other words, *regression of the foci* belonging to the primary complex *does not necessarily proceed pari passu*.

*Postmortem 1946: 335:* A woman, aged 43, died of ovarian carcinoma with metastases. In the right lower lobe, a completely calcified focus 0.2 cm. in diameter was found to be situated about 1.0 cm. below the pleural surface. A regional bronchopulmonary lymph node contained a soft, ill-defined caseous area 0.08 cm. in diameter (figure 1).

*Comment.* The difference in consistency between the primary and the lymphatic foci is particularly well shown in a postmortem roentgenogram (fig. 2). On histological examination, no evidence of recrudescence was seen, but the focus in the lymph node still showed some acid-fast rods and shadowy outlines of cells in the periphery, whereas the primary focus was completely homogeneous and devoid of acid-fast elements. Another interesting feature was the difference in size of the foci. In contrast to what is usually seen in the primary complex in childhood, the lymphatic component was much smaller than the primary focus, a finding occasionally observed in primary infection of the adult (3).

Although it might be assumed that a smaller focus would calcify more rapidly



FIGS. 1-3

than a larger one, the present instance shows that this need not be so. Moreover, the findings in this patient cannot be explained by age differences between the foci, for they belonged to the same primary complex and were the only tuberculous foci found.

*Postmortem 1446: 398:* A similar case is that of a man, aged 39, who died of Hodgkin's disease. A firmly calcified primary focus, under 0.13 cm. in diameter, was found in the left upper lobe, while the lymphatic component was 0.8 cm. in diameter, soft, caseous, and had only a pinpoint area of calcification (figure 3), as may be seen in the postmortem roentgenogram (figure 4).

Conversely, calcification may be more rapid in the lymphatic component, *i.e.*, the lesion which shows the more recent change than that observed in the preceding primary focus.

One such case is that of a young girl, aged 17, with symptoms for two months and extensive caseous cavitating tuberculosis of both lungs, which terminated in meningitis. At postmortem examination a large, peppercorn-sized, chalky, caseous primary focus was found near the diaphragmatic border of the right lower lobe, while the bifurcation lymph node was enlarged to bean size and firmly calcified. Chalky and soft caseous changes were present, only higher up, in a paratracheal lymph node.

In the cases related so far, it does not seem to be recrudescence which accounts for the differences in the quality of the foci, but simply the failure of the changes in the various foci to regress *pari passu*.

*Marked differences in quality between two foci (firmly calcified as against caseous) do not, therefore, exclude their being closely related to each other, nor do they provide evidence in themselves that the fresh looking lesion is due to new infection from without.*

#### *Cases of reinfection*

There remain a number of cases in which recent infection from without suggests itself as the most likely explanation, and it is in these cases that a fresh lesion of the primary complex type is found in a case showing another apparently older primary complex in the same organ (lung) or elsewhere. A number of such observations have been reported in the literature (7).

*Surgical Biopsy No. 1933:* A woman, aged 69, developed a large tuberculous ulcer on the dorsum of the right hand while nursing her daughter who was dying from pulmonary tuberculosis. Subsequent to the development of the ulcer of the hand, large caseous axillary lymph nodes appeared on the same side and were excised (figure 5). A roent-

FIG. 1 (Upper). Illustrates differences in the rate of regression between the primary focus and its glandular component: left, firmly calcified primary focus; right, smaller but still soft complementary focus in a corresponding lymph node.

FIG. 2 (Center). Postmortem roentgenogram of the group of foci shown in figure 1: left, firmly calcified primary focus; right, still soft lymph node complement.

FIG. 3 (Lower). Left, totally calcified primary focus; right, soft complementary focus in a corresponding lymph node with central pinpoint calcification.

genogram of the chest showed a typical calcified primary complex near the base of the right lung.

The occurrence of reinfection is also suggested when a fresh primary lesion is found in the lung of a person with firmly calcified mesenteric lymph nodes.



FIGS. 4-5

FIG. 4 (Upper). Postmortem roentgenogram of foci shown in figure 3: Left, the whole small focus calcified; right, pinpoint central calcification.

FIG. 5 (Lower). Caseous axillary lymph nodes complementary to a primary tuberculous ulcer on the dorsum of the right hand (case of true reinfection).

*Postmortem 1945: 182:* Such a case is that of a woman, aged 47, whose chest film had revealed an extensive soft mottling throughout the upper and midzone portions of the right lung, with ring shadow in the apical region. Death from tuberculous meningitis occurred soon after admission. At *necropsy*, a round well-defined completely calcified lymph node mass 2 cm. in diameter was found in the root of the mesentery. The cranial parts of the right upper lobe of the lung were occupied by an area of confluent "gelatinous" pneumonia 6 cm. in diameter. The consolidation seemed to have developed by con-

fluence of innumerable small yellowish areas of acinous and lobular infiltration, which corresponded to the mottling visible in the roentgenogram. The apical part of the consolidated area was converted into an ill-defined cavity, 3 x 2 cm. in diameter, with ragged caseous walls. There was extensive caseation of the tracheobronchial and paratracheal lymph nodes on the right side, while slight caseous stippling was seen in the bifurcation lymph node and in a few hilar lymph nodes on the left side. The abdominal organs, including the peritoneum, were peppered with miliary nodules, and there was a tuberculous meningitis.

*Comment:* A fresh lesion of the primary complex type was accompanied by a primary cavity in the right upper lobe, subsequent local spread, and the eventual development of meningitis. The old traces of primary intestinal infection make it seem virtually certain that the fresh pulmonary lesion represented a lesion of reinfection. The infiltrative process which surrounded the reinfection cavity was probably caused by bronchogenic spread from the latter and would probably have developed into "bronchogenic phthisis", were it not for the fatal meningitis.

#### *Simulation of reinfection*

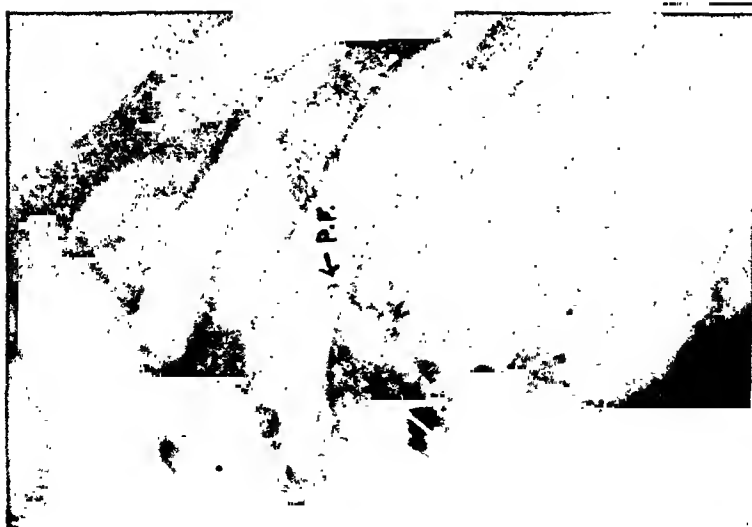
Finally, a case is presented in which a cavity, healed at the time of observation after having given rise to bronchogenic phthisis, might have been interpreted as a reinfection lesion. This interpretation was not borne out, however, by extensive histological examination of the regional lymph nodes, which failed to show any caseous changes. Instead, there were roentgenologic, as well as histopathologic, evidences of parenchymatous foci, which showed the various intermediate stages of regression between the firm calcification of the primary complex and the chalky caseous focus (healed cavity) which had caused the bronchogenic phthisis. It was, therefore, concluded in this case that the lesion which initiated phthisis was not a result of reinfection or superinfection from without, but represented a link in a continuous, endogenous, evolution from the primary complex. It was only by histological investigation that such endogenous development could be confirmed and any suspicion of an exogenous "reinfection complex" (obtained from the postmortem roentgenogram) be abandoned.

*Postmortem 1947: 30:* The patient was a 25-year-old millwright in a metal works, whose brother had died of pulmonary tuberculosis in 1932. The patient's illness began in May, 1944, and was characterized by languor and a slight cough. In November, 1944, he was found, on roentgenography, to be suffering from left-sided pulmonary tuberculosis, with extensive infiltration in the upper and midzones, and excavation in the upper zone of the lung. Calcification appeared to be present in the left hilum. The erythrocyte sedimentation rate was elevated and the sputum contained tubercle bacilli. The patient was admitted to the sanatorium on March 29, 1945, at which time his temperature was 100.4°F. His treatment consisted of a left phrenic crush and pneumoperitoneum, followed by artificial pneumothorax and pneumolysis.

Roentgenograms of the chest (April, 1945) revealed a small opacity in the outer end of the right first interspace and infiltration throughout all zones of the left lung, with ex-



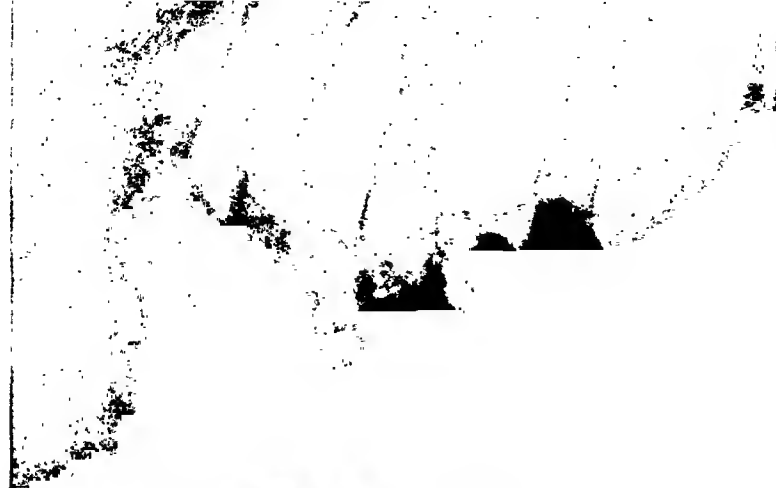
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7



8



FIGS. 6-8

cavation visible in the infraclavicular region (figure 6). Just below the cavity was a small calcified node (P.F.) and three accumulations of calcium visible at the hilum (P.H.), which were regarded as the original primary complex. In addition, there was visible just above the clavicle a small "hard" node with one or two others of a similar nature which were situated just above the calcified nodes at the left hilum. The supraclavicular node is more distinct in the film of June, 1945 (figure 7 C.F.). In the description of the pathology of these foci, presented below, it is suggested that they represent stages intermediate between the primary complex and the excavating lung lesion.

A roentgenogram obtained in June, 1945, revealed: a slight increase of opacity in the upper zone of the right lung, an elevation of the left diaphragm, and the facts that the cavity had risen towards the apex (figure 7C), and the calcified nodule just below (P.F.) was more distinct. The partially calcified intermediate or "bridge-foci" may also be seen in this film (C.F.).

A roentgenogram obtained in September, 1945, revealed the pneumoperitoneum with the elevation of the left diaphragm, almost complete clearing of the density previously visible in the upper zone of the right lung, and further elevation and considerable shrinkage of the excavation in the left lung (figure 8).

The patient, who had also been complaining of abdominal symptoms, was restless and finally asked to be discharged against advice.

In August, 1946, there was a marked extension of disease in the upper zone of the right lung and further treatment was advised but rejected. The left artificial pneumothorax was maintained.

In December, 1946, deterioration was rapid and accompanied by abdominal pain and diarrhoea, with temperatures ranging up to 102°F. The patient was admitted to hospital on January 17, 1947, and died on January 20, 1947.

At *necropsy*, the lungs showed, after fixation by formalin filling of the bronchial tree, typical bronchogenic tuberculosis with a system of cavities with thick caseous walls in the right upper lung and a plum-sized cavity in the apices of both lower lobes. The *left upper lobe* was greatly shrunken. On *postmortem roentgenography*, a firmly calcified primary complex could be made out in the midzone of the left lung, accompanied by very extensive calcification of a chain of regional lymph nodes. The primary focus itself (figure 9 P.F.) appearing firmly calcified, but was surrounded by a number of small, not so firmly calcified, nodules. In addition, there was an irregularly shaped chalky focus with a calcified shell (C), in the subapical region, and, above the chain of firmly calcified lymph node shadows (P.H.), there was a round focus visible in the hilum which suggested a focus related to a lymph node (C.F.).

On dissection, the left upper lobe revealed in its dorsocaudal parts a lentil-sized firmly calcified focus (figure 10), and in the corresponding area at the hilum there were three large bean-sized firmly calcified lymph nodes. This lesion was regarded as the primary complex.

A second group of changes was observed in the subapical ("infraclavicular") area where, 0.5 cm. below the pleural surface, an irregular, but well-defined, chalky and crumbly focus

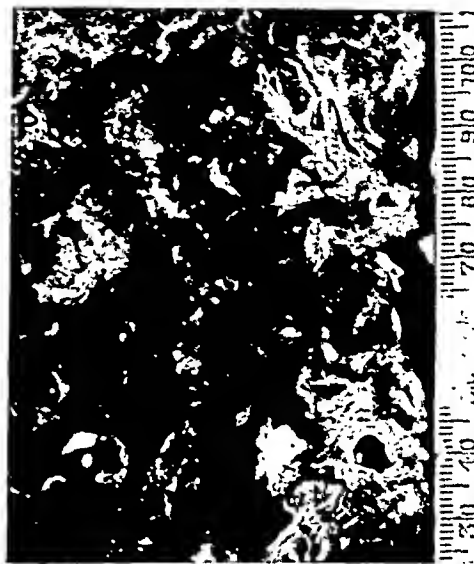
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FIG. 6 (Left). Roentgenogram April, 1945. Cavity under the left clavicle; small calcified focus just below cavity (P.F.) and calcified nodules in the hilar region (P.H.); chalky focus above hilar calcification.

FIG. 7 (Center). Roentgenogram June, 1945. Closeup of left upper lobe. Cavity (C) has risen; calcified nodule (P.F.) plainer; in addition, some chalky foci visible (C.F.) above and below clavicle.

FIG. 8 (Right). Roentgenogram September, 1945. Shows pneumoperitoneum. The cavity is grossly shrunken, raised and hardly visible.

9



FIGS. 9-11

FIG. 9 (Left). Postmortem roentgenogram: left upper lobe—P. F. Primary focus firmly calcified, but surrounded by a group of less calcified small nodules; P. H. chain of calcified primary lymph nodes; C subapical chalky focus corresponding to healed cavity. C. F. soft chalky focus in hilar region, but does not originate in lymph node. It is a small lobular caseous and calcifying chalky-focus ("bridge-focus").

FIG. 10 (Upper Right). Firmly calcified primary complex in the lower parts of the left upper lobe.

FIG. 11 (Lower Right). C: chalky focus corresponding to healed cavity. Chalky lobular caseous focus in the hilar region not shown.

was found. This lesion was 0.5 x 0.8 cm. in size and gave the appearance of a "cyst" filled with inspissated chalky-caseous material, rather than a solid focus (figure 11 C). The same material was seen to form a crumbly plug in the subapical branch of the apico-dorsal bronchus which lead to the focus. A similar but also well defined partly calcified focus, which was a little larger and corresponded to the round shadow mentioned above (figure 9 C.F.), was found in the region of the hilum at the caudal end of the lobe near the interlobar fissure. Similar foci were found scattered in the subapical region as well as in the immediate neighbourhood of the primary focus.

Histological examination of the chalky foci in the hilar region revealed remnants of elastic fibres in an alveolar pattern and in considerable numbers. This proved that these foci were unrelated to the hilar lymph nodes and did not constitute the lymph node component of a second "primary complex", i.e., a "reinfection complex". Similar findings were observed in eight other chalky foci found in the same region, which were situated in close proximity to hilar lymph nodes. In fact, apart from the firmly calcified and encapsulated primary changes, none of the numerous hilar lymph nodes subjected to histological examination showed any evidence of fresh or old caseation. Only fresh abortive tubercles, referable to the recent phthisical condition of the lung, were seen. The chalky foci provide links ("bridge-foci") between the fresh phthisical process and the firmly calcified primary complex. On histological examination, the chalky foci showed thick fibrous capsules and thick fibrous pads, rich in coal pigment, which partly replaced the foci themselves. There were also patches of calcium and calcified remnants of elastic fibres in an alveolar pattern. Ossification was observed neither in these foci nor in the lymph node complements of the primary focus, but a rim of bone trabeculae was found in the latter.

*Comment:* In an adult, aged 27, who died from bronchogenic phthisis, two sets of lesions were found in the left upper lobe. One lesion was firmly calcified and obviously represented the first manifestation of tuberculosis in this case ("primary complex"). The peripheral focus of the second lesion, which was chalky and crumbly and contained no more than patchy calcification, corresponded to a cavity first detected two years prior to death and was obviously the source of the fatal bronchogenic phthisis.

From the macroscopic appearance of this peripheral focus (6), in conjunction with a comparative survey of the roentgenograms, it apparently represented a healed cavity. The impression, however, that it constituted *at the same time* a genuine reinfection lesion, in other words a *healed reinfection cavity*, cannot be substantiated by extensive histological examination of the hilar lymph nodes. Moreover, the case provided roentgenologic, as well as morbid, anatomical evidence of links ("bridge-foci") between the primary and other foci suggesting an endogenous, possibly bronchogenic, evolution from the primary complex, rather than superinfection. This interpretation is based on what appears to be *probable* from a comparative study of the roentgenologic and histopathologic aspects of the case. In view of the uncertainty in assessing the age of tuberculous foci (*vide supra*) different interpretations are *possible*. Exogenous superinfection, for example, as the source of the healed cavity can neither be proved nor disproved from the evidence available. What has been interpreted as "bridge-

foci" between the primary complex and the healed cavity could theoretically constitute bronchogenic changes following cavitation. Such an explanation takes no account of the close proximity of one group of these chalky nodules to the primary focus and is therefore unlikely.

At all events, the case again shows the difficulties and pitfalls of the clinical and anatomical diagnosis of reinfection and its rôle in the causation of phthisis. It demonstrates the necessity of establishing the presence of appreciable caseous changes in the lymph nodes tributary to the parenchymatous complement of the suspected second lesion of the "primary complex" type. Intensive histological examination may be required to establish the lymphatic nature of a suspected caseous lymph node.

The observations presented seem to be significant *clinically* in that they demonstrate again the difficulties in assessing the real age of tuberculous changes, whether calcified or not. Changes which appear to be recent have been shown to originate in an obsolete focus and related lesions may present very different degrees of "freshness". The diagnosis of reinfection or superinfection often rests with the simple clinical impression that a lesion must be exogenous because of the calcified state of the other changes present. In such cases, however, post-mortem and histological investigation is needed in order to exclude a source from within.

#### SUMMARY

In the diagnosis of reinfection in tuberculosis, the following sources of error may arise: (1) endogenous origin of recent looking changes from an obsolete lesion; or (2) delayed calcification of both parts or asynchronous calcification of one constituent of the primary complex.

Examples of both of the above types of lesion are presented, and also a case in which reinfection was closely simulated in the clinical and postmortem roentgenograms and only disproved by histological examination of the hilar lymph nodes.

#### SUMARIO

##### *Patología de la Reinfección*

En el diagnóstico de la reinfección en la tuberculosis, pueden intervenir las siguientes causas de error:

(1) Origen endógeno de alteraciones aparentemente recientes de una lesión antigua.

(2) Calcificación tardía de ambas partes, o asincrónica de uno de los componentes, del complejo primario.

Se presentan ejemplos de (1) y (2), y además un caso en el que las radiografías obtenidas *intra vitam* y en la autopsia simulaban estrechamente reinfección refutándolas únicamente el examen histológico de los ganglios linfáticos del hilio.

#### *Acknowledgments*

The authors wish to record their indebtedness to Dr. A. L. Woolf for help with post-mortem roentgenography and revision of the manuscript, and to J. E. Mayhew, L. Sprain and Miss B. Buckle for technical assistance.

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# SARCOIDOSIS FOLLOWING PRIMARY TUBERCULOSIS

## A Case Report

JOSEPH S. HIATT, JR.

In a recent editorial, Pinner (1) has reviewed the present day opinions concerning the etiology of Boeck's sarcoid. There are still wide differences of opinion concerning the nature of sarcoid disease and these differences form the basis for a somewhat confused and complex picture. Sweany (2) contends that Boeck's sarcoid is a distinct disease entity which is not related to tuberculosis. In contrast to this belief, Pinner (3) has long held that sarcoidosis is a form of non-caseating tuberculosis and many workers, particularly in the field of tuberculosis, have favored this opinion.

The writer has observed patients who showed no reaction to tuberculin and presented the lymph node findings of sarcoidosis, who later subsequently developed a positive tuberculin reaction, a change in the lymph node biopsy findings, and the characteristic picture of frank tuberculosis. The present communication is concerned with a case in which the existence of primary tuberculosis was established before characteristics of sarcoidosis appeared and in which rapid clearing of the sarcoid lesions occurred. It is believed that this case is an unusual instance and may possibly afford evidence that sarcoidosis is a disease of nontuberculous etiology. No attempt has been made to present a survey of the literature on sarcoidosis as it has been adequately covered previously in several papers, including that by Hogan (4).

## CASE REPORT

H. H., a 10-year-old Negro girl, was admitted to the North Carolina Sanatorium June 4, 1944. She had been found to have a positive tuberculin reaction during a school survey a few weeks previously, and a subsequent roentgenogram of the chest revealed a typical picture of primary tuberculosis. She had always been a healthy child and there was no known exposure to tuberculosis. There had been no weight loss, nor symptoms referable to the cardio-respiratory tract.

The admission physical examination revealed a well developed and nourished Negro girl who did not appear ill. There were no abnormal physical findings.

The first roentgenogram after admission to the sanatorium (figure 1) showed a small "BB size" nodular density within the circle of the first rib anteriorly on the right. Over the inner zone of the lung from the level of the third to the eighth interspace posteriorly, there was a large area of stippled nodular density representing partially calcified lymph nodes. The left lung field revealed nothing abnormal. This film demonstrated the same changes as the original survey film. A tuberculin test (O. T. 1:10,000) was positive. Urinalysis and stool examinations were normal. Repeated twenty-four hour specimens of sputum, obtained by forceful coughing, were negative for tubercle bacilli.

The hemoglobin was 83 per cent (Sahli) and the erythrocyte count 4,160,000 per cu. mm. The total leucocyte count was 7,300 per cu. mm. with the following differential count: polymorphonuclear 70 per cent; small lymphocytes 27 per cent; large lymphocytes 1 per cent; eosinophiles 1 per cent; and monocytes 1 per cent. The erythrocytes appeared normal on fresh and stained smears. No sickling was noted. A serologic test for syphilis (Kline) was

<sup>1</sup> North Carolina Sanatorium, McCain, North Carolina.

negative and the erythrocyte sedimentation rate was 70 minutes (Linzenmeier method).

The patient was placed upon a modified rest regimen and throughout her stay was clinically asymptomatic. The temperature, pulse, and respiration remained within normal limits. A subsequent chest roentgenogram revealed no change and she was discharged October 30, 1914, classified as primary tuberculosis, arrested. There had been a weight gain of five lbs.

After discharge, the patient continued to have periodic fluoroscopic and roentgenologic examinations of the chest. The lesions remained unchanged until a roentgenogram of the chest in January, 1917, revealed extensive new densities and she was readmitted to the sanatorium, February 23, 1917. She had no specific complaints, but had lost a small amount of weight during the preceeding four weeks. There had been no known exposure to tuberculosis during the interval at home.

Physical examination showed a 13-year-old Negro girl in excellent nutritional status and who did not appear to be ill. Her temperature, pulse, and respirations were normal. There was a generalized lymphadenopathy, the nodes being moderately enlarged, freely movable and nontender. A few fine moist râles, most of which disappeared after coughing, were heard in the right upper lung field and to a lesser degree on the left. By percussion, there was increased retro-mammary dullness.

Roentgenogram of the chest on this admission (figure 2) showed increased linear and nodular densities throughout both lung fields with markedly enlarged bilateral hilar shadows. The previously present calcified densities were visible and appeared unchanged. A tuberculin test (O. T. 1:10,000) was positive. A skin test to histoplasmin gave no reaction. Two gastric lavage cultures yielded no growth of tubercle bacilli. On admission, the hemoglobin was 78 per cent (Sahli) and the erythrocyte count 3,920,000 per cu. mm. The leucocyte count was 5,200 per cu. mm. with a differential count as follows: polymorphonuclear 63 per cent; small lymphocytes 32 per cent; eosinophils 1 per cent; and monocytes 3 per cent. There was no sickling of the erythrocytes. The erythrocyte sedimentation rate was 25 minutes (Linzenmeier method).

Shortly after admission, a left epitrochlear lymph node was removed for study.<sup>2</sup> The report is as follows:

"In multiple sections of this small lymph node there is considerable scarring evident in the interstitium and at the capsular surface. One pole is entirely occupied by a mass of tubercles which in many instances are conglomerate. These tubercles are composed entirely of epithelioid cells with a slight fluid exudation in their centers, and with a lymphocytic infiltration both at the centers and at the periphery. No giant cells are found and no actual caseation is found at any point. In the opposite pole there is considerable fluid exudation into the interstitial tissues but no lesions otherwise are noted here.

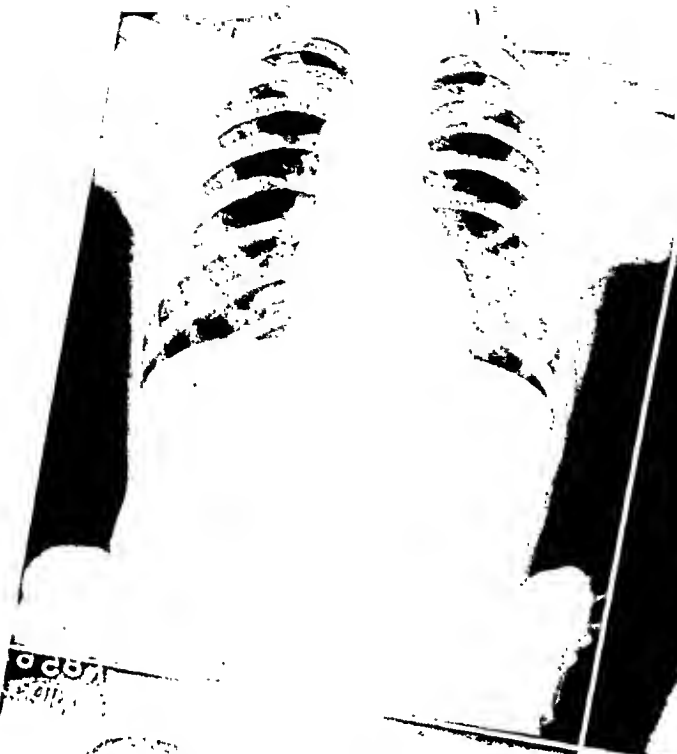
The lesions in this node are entirely consistent with the diagnosis of Boeck's sarcoid but the presence of an actual non-caseating type of tuberculous infection cannot be ruled out, even though we have been unsuccessful in staining the organisms in this case. With other findings and with history consistent with Boeck's sarcoid, these findings would support such a diagnosis."

Throughout her stay the patient was asymptomatic and gained thirteen and one-half pounds in weight. Six weeks after admission a repeat roentgenogram (figure 3) showed considerable clearing and an attempt was made to repeat the lymph node studies, but there had been complete disappearance of the lymphadenopathy and no node could be obtained for biopsy. Repeated fluoroscopic studies showed no evidence of cystic changes in the small bones of the hands and feet. There were no demonstrable skin lesions at any time. A chest roentgenogram taken shortly before discharge (figure 4) showed marked clearing of the densities in both lung fields and decrease in extent of the hilar shadows. The patient was discharged June 1, 1917, to continue under close medical supervision and to avoid strenuous activity.

<sup>2</sup> Biopsy studies done by Dr. Thomas N. Lide, Pathologist, North Carolina Sanatorium, McCain, North Carolina.



JOSEPH S. HIATT, JR.



## COMMENT

The roentgenologic changes on the second admission of this patient were very extensive and represented a process apparently superimposed on previously established calcific primary tuberculosis. Possible causes of the illness, such as a fungus infection, a lymphoma, sarcoidosis, miliary tuberculosis, or reactivated primary tuberculosis were all considered. The clinical diagnosis of sarcoidosis was subsequently supported by lymph node biopsy studies. Within a relatively short period of time, there was marked clearing of the chest lesions and complete disappearance of the generalized lymphadenopathy with a gain in weight and further improvement in the nutritional status of the patient.

## SUMMARY

The development of sarcoidosis, confirmed by biopsy following arrested primary tuberculosis, is reported. It is believed that this sequence of events represents an unusual situation. No similar case has been previously seen in this institution, where a considerable number of cases of sarcoidosis are seen and studied each year.

## SUMARIO

*Sarcoidosis Consecutiva a Tuberculosis Primaria: Historia Clínica*

La aparición de sarcoidosis, confirmada por la biopsia, a continuación de una tuberculosis primaria estacionada, parece ser una situación extraña. En el establecimiento del A., donde observan y estudian un número considerable de casos de sarcoidosis todos los años, no habían observado antes ningún caso semejante.

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FIG. 1. (Upper left). Chest roentgenogram of a 10-year-old Negro girl on first admission to the North Carolina Sanatorium June 5, 1944. Calcified densities right lung field representing primary tuberculosis. Tuberculin positive 1:10,000.

FIG. 2. (Upper right). First chest roentgenogram on second admission to the North Carolina Sanatorium February 24, 1947. Bilateral hilar enlargement, miliary distribution finely nodular and linear densities throughout both lung fields. Calcified densities unchanged. Tuberculin positive 1:10,000. Skin test to histoplasmin gave no reaction. Lymph node biopsy shows sarcoidosis.

FIG. 3. (Lower left). Chest roentgenogram made April 8, 1947, forty three days after second admission, shows regression of hilar lymphadenopathy and clearing of peripheral lung field densities. No peripheral lymph nodes palpable at this time, biopsy could not be repeated.

FIG. 4. (Lower right). Chest roentgenogram just before discharge May 27, 1947, reveals almost the same findings as on first admission in 1944.

# CORRELATION OF THE RADIOACTIVITY OF SUSPENSIONS OF TUBERCLE BACILLI WITH THEIR TURBIDITY<sup>1</sup>

Method of estimating weight in doses of tubercle bacilli

A. KAPLAN, J. TRAUM AND R. A. BANKOWSKI<sup>2</sup>

The dosage of tubercle bacilli used in experimental and other studies has a very important bearing on the interpretation of results of animal inoculations and, hence, the methods of estimating dosage have received considerable attention from those interested in the work. With few exceptions, dosages mentioned in the literature are expressed in terms of milligrams based upon the weight of tubercle bacilli from which as much moisture as can be absorbed by blotting paper has been removed. The direct microscopic count is sometimes used in estimating dosage and even then the values obtained from such determinations are often transposed to milligrams of organisms. Most workers have recognized that inherent sources of variations in these methods are great. One text book (1), in the discussion of standard dosages based on weight and subsequent dilutions, contains the statement, "However the amount of water which can be removed by such procedure is so variable that only the barest approximation to accuracy can be expected."

The production of radioactive tubercle bacilli made available a unique method for determining the amount of bacilli in a suspension. This procedure is not difficult to accomplish in a laboratory which has facilities and materials for the growth of radioactive organisms and the equipment for the measurement of radioactivity. It is apparent, however, that, in order to be useful, a method should not be confined to the special apparatus and radioactive salts necessary in this procedure, but should be applicable to equipment and materials available to most laboratories. With this in mind, suspensions of radioactive, acid-fast bacilli were prepared, the weight of bacilli in suspension was determined from its radioactivity, and the concentration of the suspension was correlated with its turbidity. The turbidity of these suspensions of known concentration was measured by three standard laboratory procedures: the photometric, the McFarland's nephelometric (2), and Gates' opacimetric (3), methods. Thus data were obtained which correlated the concentration of a bacterial suspension with its opacity.

The Gates opacimeter and McFarland nephelometer have been used for many years to estimate the turbidity of bacterial suspensions. In recent years, however, the photoelectric cell has been employed for this purpose (4 to 10). The photoelectric cell has several advantages over visual methods for estimating turbidity: (1) it permits accurate determination of light intensities, (2) it is much more sensitive than the eye to small variations in light intensities, (3) it

<sup>1</sup> Supported in part by grants from the National Tuberculosis Association.

<sup>2</sup> From the laboratories of the Department of Veterinary Science, Agricultural Experiment Station, and of the Division of Physiology of the Medical School, University of California, Berkeley, California.

eliminates the subjective errors that are encountered frequently in visual methods.

As dosages of tubercle bacilli are most frequently expressed in milligrams, the opacity of a bacterial suspension should depend upon the weight of bacilli in suspension. According to Wilson (4) and Alper and Sterne (5), the turbidity of bacterial suspensions is a more accurate index of the weight or size of bacilli than of the number. Wilson (4) states that opacity methods measure the total quantity of bacterial protoplasm in suspension, and not the number of organisms. This is consistent with the results of Fitch and his co-workers (11), who found that the concentration of *Brucella abortus* antigens can be estimated more accurately by measuring the volume of bacteria after centrifugation than by employing visual turbidimetric methods. Roepke and Fitch (10) later found that turbidity measured by means of a photometer gave satisfactory results.

#### EXPERIMENTAL

**Bacterial cultures:** Radioactive, acid-fast bacilli were produced by growing *Mycobacterium phlei* and the H37 and BCG strains of tubercle bacilli in liquid media containing approximately one micro curie of radioactive phosphorus per cc. A small film of a young culture of bacilli growing rapidly in the Sauton medium was transplanted to Sauton media containing radioactive phosphorus in the form of a neutral solution of  $\text{Na}_2\text{HPO}_4$ . Erlenmeyer flasks (225 cc. capacity) containing 75 cc. of medium served as culture flasks. Cultures of *Mycobacterium phlei* were harvested on the fourth and sixth days while the H37 and BCG strains of tubercle bacilli were collected on the seventeenth, twenty-third, and thirty-fourth days after planting.

**Bacterial suspensions:** The bacilli were collected by filtering on a Buchner funnel and were washed several times with 0.9 per cent sodium chloride solution. The bacteria were transferred to a mortar, ground very thoroughly and then suspended in a solution consisting of equal parts of phosphate buffer, pH 7.4, and physiological saline solution. The larger clumps of bacilli were eliminated by allowing the suspension to stand for five minutes and then decanting the upper portion of the suspension upon a Buchner funnel. The rest of the suspension was discarded while the fine residue on the filter was subjected to further grindings and washings, which were repeated six times. The washed bacilli were then centrifuged for five or ten minutes at approximately 1,000 r.p.m. The supernatant fluid was taken for turbidity and radioactivity measurements.

**Measurement of turbidity:** Seven or eight different dilutions were prepared from the above suspensions by diluting them with phosphate buffer. The radioactivity of each suspension series was determined and from this the amount of bacilli was calculated. The turbidity of each series was measured by the photometer<sup>3</sup>, Gates opacimeter and McFarland nephelometer. The Cenco No. 1 and Cenco Aklos filters were used in the photometer. The opacimeter readings were obtained in daylight in front of a large window with the tube held over a black background. Comparisons were made in daylight.

**Determination of weight by radioactivity of bacilli in suspension:** The weight of bacilli in suspension was determined from the radioactivity of fresh bacilli and of the suspension. This was carried out in the following manner:

- (a) The bacteria were filtered on a Buchner funnel and washed once with distilled water, as much moisture as possible was removed by applying suction to the system. Portions of the bacteria on the filter paper were placed in tared vials, weighed, and dehydrated by heating for twenty-four hours at 95° C. in a vacuum oven. The material was weighed again and the radioactivity of the dehydrated residue was measured.

<sup>3</sup> Indicates the radioactive atom p 32.

<sup>4</sup> Cenco-Shepard Sanford photometer.

- (b) The radioactivity of aliquot portions of several dilutions in the suspension series was measured.
- (c) The corresponding suspensions were filtered through Gradocol membranes of 400 mu porosity. The radioactivity of known volumes of filtrates was measured. These values represented the amount of radioactivity in the suspension mixtures that were not associated with the bacilli themselves.

TABLE 1

*Relation between the concentration and turbidity of suspensions of Mycobacterium phlei*

AGE OF CULTURE	MG. OF BACILLI PER CC. OF SUSPENSION		TURBIDITY READINGS		
	Dehydrated weight*	Fresh weight**	Photometer	Gates	McFarland
4 days	0.175	0.65	34.8	2.8	2.75
	0.12	0.45	47.2	4.1	1.4
	0.070	0.26	63.5	6.1	0.75
	0.044	0.16	72.5	7.8	0.5
	0.035	0.13	78.0	8.5	0.4
	0.018	0.067	88.0	13.5	
	0.011	0.041	91.0	—	
6	2.00	7.66	2.2	0.9	
	1.40	5.35	3.2	1.1	
	1.00	3.83	5.2	1.2	
	0.50	1.92	12.1	1.5	
	0.20	0.77	32.5	2.5	4.0
	0.10	0.38	54.3	3.3	2.75
	0.050	0.19	72.0		0.9

\* Weight after dehydration for twenty-four hours at 95°C. in a vacuum oven.

\*\* Weight after drying on a Buchner funnel.

(d) Calculations:

Let S = total radioactivity per cc. of suspension;

F = radioactivity per cc. of filtrate after passing suspension through Gradocol membrane;

B = radioactivity per mg. of dehydrated bacilli;

D = per cent of dehydrated residue in fresh bacilli

Then the mg. of bacilli (dehydrated weight) per cc. of suspension =  $\frac{S - F}{B}$ , and

The mg. of bacilli (fresh weight) per cc. of suspension =  $\frac{S - F}{B} \times \frac{100}{D}$

In the suspension examined, the weights were found to be in close proportional agreement with the weight of the concentrated suspension.

A control experiment was performed in which the concentration of bacilli suspended in distilled water was determined both by radioactive methods and by direct weighing after evaporation of the water. Good agreement was obtained between the two methods.

## RESULTS

The relation between the weight of bacilli in suspension and the turbidity of suspensions of *Mycobacterium phlei*, and the BCG and H37 strains of *M. tuberculosis*, is shown in tables 1, 2 and 3 respectively. Nine different suspensions

TABLE 2

*Relation between the concentration and turbidity of suspensions of the BCG strain of tubercle bacilli*

AGE OF CULTURE	MG. OF BACILLI PER CC. OF SUSPENSION		TURBIDITY READINGS		
	Dehydrated weight*	Fresh weight**	Photometer	Gates	McFarland
<i>days</i>					
23	0.98	3.21	4.1	1.3	
	0.49	1.61	12.0	1.8	
	0.25	0.82	25.5	2.4	2.75
	0.17	0.56	37.0	3.2	1.8
	0.12	0.39	49.5	3.9	1.4
	0.098	0.32	53.0	5.0	0.9
	0.049	0.16	72.3	8.1	0.5
	0.029	0.095	80.8	9.3	
	0.010	0.033	91.0		
17	0.945	3.28	4.5	0.9	
	0.47	1.64	11.1	1.3	
	0.24	0.82	23.7	2.0	3.5
	0.19	0.66	29.9	2.3	3.1
	0.13	0.46	41.0	3.0	2.3
	0.095	0.33	50.0	4.0	1.8
	0.047	0.16	71.0	7.0	0.9
17	0.32	0.95	17.0	1.7	
	0.22	0.66	26.0	2.1	3.5
	0.16	0.47	35.5	2.8	2.3
	0.13	0.38	42.0	3.1	2.3
	0.064	0.19	62.8	5.6	1.1
	0.048	0.14	70.0	6.9	0.8
	0.032	0.095	77.5	9.0	0.5
34	1.97	6.45	2.0	0.8	
	0.49	1.61	11.5	1.4	
	0.39	1.29	15.0	1.6	
	0.28	0.90	22.5	2.0	4.0
	0.20	0.65	31.5	2.4	3.25
	0.14	0.46	42.5	3.2	1.8
	0.099	0.32	53.5	4.3	1.6
34	0.46	1.53	12.1	1.5	
	0.23	0.76	27.0	2.2	3.5
	0.092	0.31	53.8	4.3	1.6
	0.055	0.18	68.0	7.2	0.8
	0.046	0.15	72.2	8.2	0.6
	0.032	0.11	79.0	9.2	
	0.023	0.076	83.5		

\* Weight after dehydration for twenty-four hours at 95°C. in a vacuum oven.

\*\* Weight after drying on a Buchner funnel.

were employed. The ages of the cultures varied from four to thirty-four days. *Results with the photelometer:* The dehydrated weight of bacilli in milligrams is plotted against photelometric readings in figure 1. A smooth curve is obtained with only minor deviations. In estimating the concentration of a suspension by its opacity, as measured by a photelometer, the error would rarely exceed 10 per cent if the concentrations were such that measurements fell on the central part of the scale. It should be noted that the curve is almost linear (on a semi-logarithm scale) between readings of 25 and 70 or bacterial concentrations between 0.25 and 0.05 mg. of dehydrated weight per cc. The slope changes at these points and the curve is less reliable beyond this range.

TABLE 3

*Relation between the concentration and turbidity of suspensions of the H37 strain of tubercle bacilli*

AGE OF CULTURE	MG. OF BACILLI PER CC. OF SUSPENSION		TURBIDITY READINGS		
	Dehydrated weight*	Fresh weight**	Phtelometer	Gates	McFarland
Days	0.24	1.00	24.5	2.0	3.5
	0.19	0.80	33.0	2.9	2.9
	0.15	0.60	42.0	3.4	1.9
	0.12	0.50	47.0	4.0	1.5
	0.097	0.40	53.2	5.1	1.3
	0.073	0.30	60.2	6.9	1.1
	0.049	0.20	70.2	9.0	0.8
20	0.110	0.46	48.0	3.8	1.5
	0.090	0.37	53.5	4.7	1.4
	0.078	0.32	57.9	5.0	1.3
	0.067	0.28	61.8	5.9	1.2
	0.056	0.23	61.6	7.0	1.1
	0.045	0.19	70.6	8.4	0.75
	0.034	0.14	77.0		0.60

\* Weight after dehydration for twenty-four hours at 95°C. in a vacuum oven.

\*\* Weight after drying on a Buchner funnel.

In figure 2, the photelometer readings of the same suspensions are plotted against weights of bacteria, but in this case the concentration is expressed in terms of the fresh weight of bacilli instead of the dehydrated weight. It should be noted that "fresh weight" applies to the weight of bacilli filtered on a Buchner funnel from which water was removed by applying suction for a short period of time. It is obvious that drying in this manner is not constant and that a source of error is introduced. In view of the general practice, however, of expressing the concentration of suspensions of tubercle bacilli in terms of fresh weight, such weights are plotted against photelometer readings in figure 2. The curve has the same general shape as that in figure 1, but the spread in values is larger. The deviation of the points from the best fitting curve is greater than in figure 1.

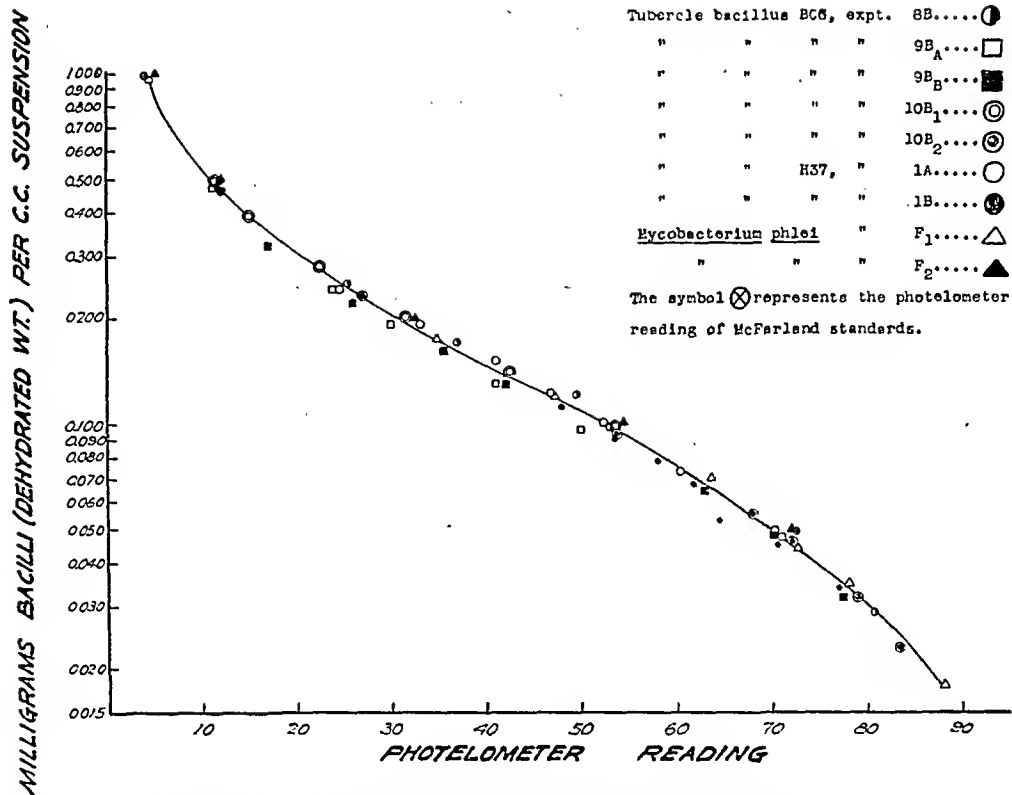


FIG. 1. The milligrams of acid-fast bacilli (weight after dehydration in a vacuum oven) per cc. of suspension are plotted against turbidity as measured by the photometer.

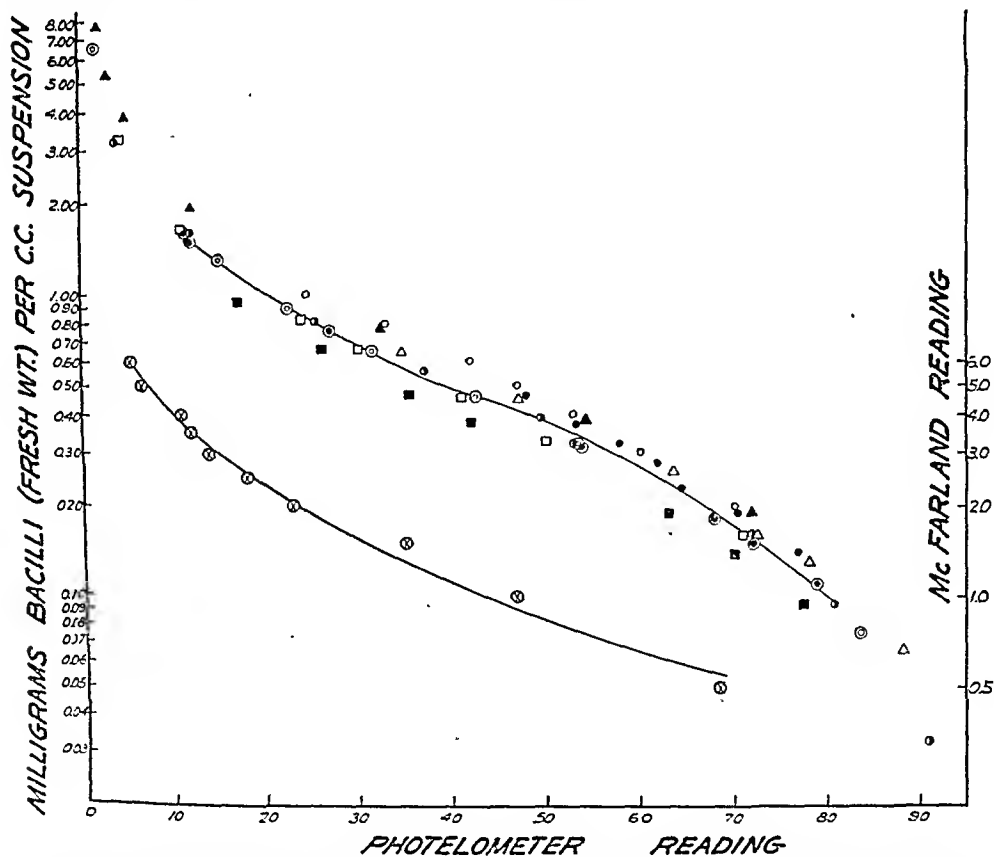


FIG. 2. The milligrams of acid-fast bacilli (fresh weight) per cc. of suspension are plotted against turbidity measured by the photometer. The left scale ordinate indicates the weight of bacilli, while the right scale ordinate indicates the McFarland reading. The symbols are the same as in figure 1.



The lower curve in figure 2 represents the relation between McFarland reading and photometer reading. In this way a relation between McFarland reading and concentration of bacilli in suspension can be obtained. For example, an estimation of the concentration of bacilli with an opacity corresponding to that

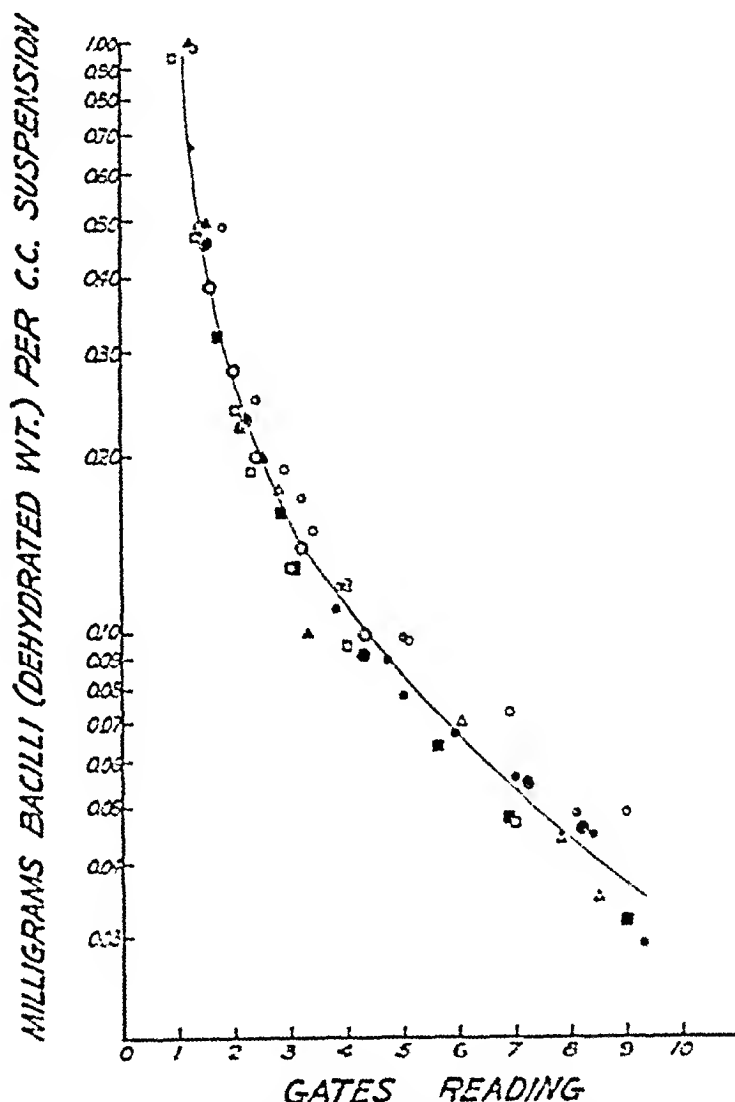


FIG. 3. The milligrams of acid-fast bacilli (dehydrated weight) per cc. of suspension are plotted against turbidity as measured by the Gates' opacimeter. The symbols are the same as in figure 1.

of a McFarland standard 1.0 can be made by taking the point on the lower curve that is located at McFarland reading of 1.0 and then proceeding vertically until the upper curve is intersected. The reading on the left scale (0.44) provides the concentration of the suspension in terms of mg. of bacilli per cc.

*Results with the Gates opacimeter:* The concentration of bacilli, expressed as dehydrated weight per cc. in milligrams was plotted in a similar fashion against turbidity readings obtained with the Gates opacimeter in figure 3. It can readily be seen that, even though the Gates opacimeter is neither as consistent nor as

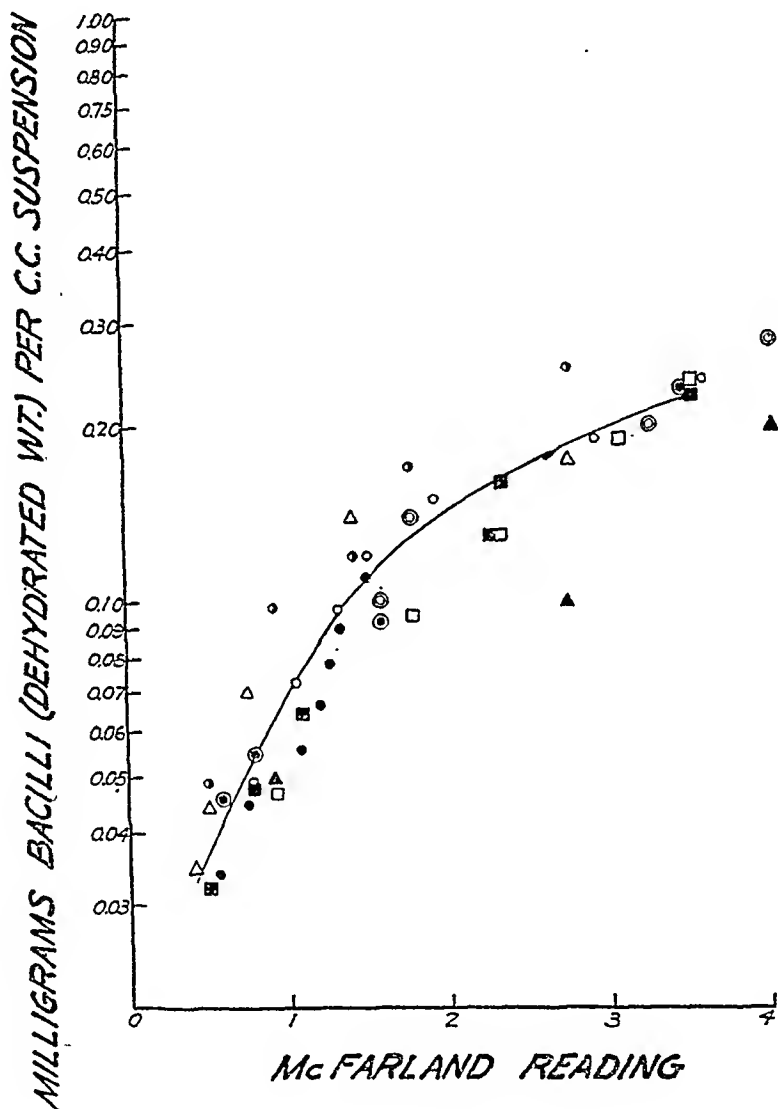


FIG. 4. The milligrams of acid-fast bacilli (dehydrated weight) per cc. of suspension are plotted against turbidity as measured by the McFarland nephelometer. The symbols are the same as in figure 1.

accurate as the photometer, a general relation between turbidity and concentration is nevertheless observed. As the readings with the Gates opacimeter are dependent to a large degree upon the sensitivity of the eyes of the observer, results obtained by different individuals may be variable.

*Results with the McFarland nephelometer:* These were disappointing. As shown in figure 4, considerable variability was encountered. In order to make a correlation between weight and turbidity available to laboratories where the nephelometer is widely used, however, several series of McFarland standards were prepared, using the precautions of Roepke and Fitch (9), and the turbidities of these standards were measured by the photometer. This relation between photometer reading and turbidity of McFarland standard is represented by the lower curve in figure 2. Thus a correlation between McFarland reading and fresh weight of bacilli in a suspension is available.

#### SUMMARY

1. A method is described by which the weight of radioactive tubercle bacilli in a suspension can be determined by measurements of their radioactivity.

2. The relation between the weight of acid-fast bacilli in suspension and turbidity as measured by the photometer, Gates opacimeter and McFarland nephelometer is presented.

3. The photometer provides a convenient and reasonably accurate method for estimating the weight of acid-fast bacilli in suspensions. Consistent results were obtained with three types of acid-fast bacilli, namely, *Mycobacterium phlei* and BCG and H37 strains of *Mycobacterium tuberculosis*.

#### SUMARIO

*Correlación de la Radioactividad y la Turbidez de las Suspensiones de Bacilos Tuberculosos. Técnica para Calcular el Peso en Dosis de Bacilos*

1. Describese una técnica que permite determinar el peso de los bacilos tuberculosos en una suspensión por medio de mediciones de su radioactividad.

2. Preséntase la relación entre el peso de los bacilos acidorresistentes en suspensión y la turbiedad medida con el fotómetro, el opacímetro de Gates y el nefelómetro de McFarland.

3. El fotómetro facilita un método conveniente y bastante exacto para calcular el peso de los bacilos acidorresistentes en suspensión. Obtuvieron resultados compatibles con tres tipos de bacilos acidorresistentes, a saber: *Mycobacterium phlei*, y cepas de BCG y H37 del *Mycobacterium tuberculosis*.

#### Acknowledgment

The authors take this opportunity to thank Dr. I. L. Chaikoff, of the Division of Physiology of the Medical School, University of California, Berkeley, California, for his advice and interest in the work and for permission to use the facilities of his laboratory.

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# STREPTOMYCIN IN EXPERIMENTAL GUINEA PIG TUBERCULOSIS<sup>1</sup>

M. I. SMITH, E. W. EMMART AND W. T. McCLOSKEY

## INTRODUCTION

In all of the studies previously reported from this laboratory on the chemotherapeutic action of streptomycin in experimental tuberculosis in animals, treatment was begun the day of, or the day after, infection and continued uninterruptedly for ten to twelve weeks until the majority of the untreated controls died. At this point the experiments were terminated and the value of the particular treatment appraised. Under such a regimen, treatment with graded doses of streptomycin indicated a roughly proportional relationship of dose and effect. The highest dose employed under these experimental conditions, 40 mg/kg given intramuscularly in divided doses twice daily, gave a very substantial degree of protection. Forty per cent of the animals were free from macroscopic tuberculosis, and only minimal lesions were present in the remainder (1).

The present report consists of the results of treatment with this optimal dose of streptomycin, 20 mg/kg twice daily, when treatment was continued for shorter periods, namely, one, two and four weeks as compared with eleven weeks. Treatment was started in all cases the day of infection and continued five days weekly with a double dose on the fifth day. It seemed desirable to determine whether intensive treatment during the first weeks of infection, before the tissues are generally invaded by the tubercle bacilli, would or would not be as effective in suppressing the disease as the much longer periods of treatment. In addition, experiments were set up in which treatment was postponed for one, two, three and four weeks after infection in order to determine whether prolonged treatment with streptomycin would be effective in eradicating the already established disease, as it is in preventing the disease when treatment is begun immediately after infection.

It may be pointed out at this time that the type of experimental infection which is used in this laboratory results in a generalized miliary tuberculosis which progresses rapidly to a fatal issue usually within forty to ninety days.

The chemical structure of streptomycin is as yet unknown. However, analysis of the degradation products of streptomycin (2, 3) appears to indicate that inositol may be considered as the nucleus around which the streptomycin molecule is built. Moreover, inositol was isolated from the tubercle bacillus by Anderson (4) and theoretically it could be regarded as an essential metabolite, and, if so, streptomycin might be considered as an antagonistic analogue of the essential metabolite inositol.

Experiments in this laboratory on the influence of inositol on the growth of the tubercle bacillus strain A27 *in vitro* in Kirchner's medium showed no effect in concentrations up to 1 per cent. When various concentrations of streptomycin were studied *in vitro* with inositol up to 1 per cent, there was no indication that

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the tuberculostatic activity of the antibiotic was antagonized. Similar results were obtained with the rapidly growing strain 607 in submerged cultures in Dubos medium. Nevertheless, in view of the above considerations, it seemed desirable to determine the effect of inositol in experimental guinea pig tuberculosis and to ascertain what effect it has on the chemotherapeutic efficacy of streptomycin when the two drugs were administered together.

#### EXPERIMENTAL

One hundred and ten male guinea pigs, weighing 250 to 300 gram, were inoculated intraperitoneally with 1.0 cc. of a suspension of tubercle bacilli human strain H37Rv containing 0.5 mg. moist weight of the organisms. They were divided into 11 equal groups.

The first 4 groups received daily intramuscular injections of 40 mg/kg streptomycin divided into 2 equal doses for five days a week with a double dose on the fifth day. Treatment was begun the day of infection. The length of treatment of the 4 groups was: group A, one week; group B, two weeks; group C, four weeks; and group D, eleven weeks. Group E served as controls.

The next series of 4 groups received the same daily dose of streptomycin as in the foregoing 4 groups, but were all treated alike for a period of eleven weeks. In this series, the interval between infection and the beginning of treatment was varied as follows: group F, one week; group G, two weeks; group H, three weeks; and group I, four weeks.

Of the remaining 2 groups, N received the same streptomycin treatment as group I, but in combination with 0.1 gm/kg of inositol with each dose of streptomycin, and group L was given inositol alone, at the same dose level. Treatment was begun the day of infection.

All the animals were weighed once a week. At death they were autopsied, the extent of tuberculous involvement noted and graded as previously described (5). Three months after infection, when 9 of the 10 controls died, the survivors were tuberculin tested with .01 mg. PPD in 0.1 cc. saline injected intracutaneously. The experiment was terminated 133 to 148 days after infection when all the survivors were killed with chloroform, autopsied and the amount of tuberculosis noted. In doubtful instances, smears were made from suspicious materials for Ziehl-Neelsen stain. In the absence of any gross evidence of tuberculous infection, suspensions of the finely minced spleens were made in 5.0 cc. sterile physiological saline and the supernatant fluid used; (a) for culturing on Steenken and Smith's medium (6), and (b) for inoculation into the right groin of each of 2 guinea pigs which were tuberculin tested and autopsied six weeks later. About 0.1 cc. of the suspension was used for culturing and 1.0 cc. for inoculation per guinea pig. Only those animals which were free from tuberculosis by all the criteria employed were rated zero.

#### RESULTS

*Variation in the length of treatment:* Treatment with streptomycin<sup>2</sup> for one and two weeks following infection had no significant effect on the degree and extent of tuberculous involvement, as shown in groups A and B, table 1. Four weeks of treatment definitely reduced the extent of disease by about one-half (C, table 1). Prolongation of life however, was evident in all three groups and the average

<sup>2</sup> Blood analysis of normal guinea pigs receiving single injections of streptomycin intramuscularly showed on an average the following concentrations of streptomycin in the serum, expressed as units per cc.:

Dose units/kg.	1 hr.	2 hrs.	3 hrs.	4 hrs.	5 hrs.	6 hrs.	7 hrs.	18 hrs.
20,000	13.2	10.8	6.2	4.0	1.8	0.8	0.5	0.2
40,000	37.0	25.5	13.2	7.8	4.8	3.2	2.9	1.9

The analyses were made by a turbidimetric method using *B circulans* as the test organism.

gain in weight, as well as the percentage reduction in mortality, were definitely related to the length of time of treatment (A, B and C, table 2; figure 1). When treatment was continued for eleven weeks all the animals survived, showed normal weight gains, and 4 of the 10 animals appeared free from lesions, though 7 out of the 10 reacted positively to tuberculin (group D, tables 1 and 2; figure 1). It should be emphasized that intensive treatment with streptomycin during the incubation period of the disease only prolonged life, but did little to check the

TABLE 1

*Index numbers<sup>1</sup> indicating extent of tuberculous involvement in individual guinea pigs in each of eleven groups after being given specified treatment for stated periods of time and after stated intervals between infection and treatment*

ANIMAL NUMBER	CON- TROL GROUP E NO TREAT MENT	TREATMENT WITH STREPTOMYCIN BEGINNING THE DAY OF INFECTION AND CONTINUING THE SPECIFIED NUMBER OF WEEKS				TREATMENT WITH STREPTOMYCIN BEGINNING SPECIFIED NUMBER OF WEEKS AFTER INFECTION AND CONTINUING FOR ELEVEN WEEKS				TREATMENT WITH STREP- TOMYCIN AND INOSITOL BE- GINNING FOUR WEEKS AFTER INFECTION AND CONTINUING 11 WEEKS, GROUP N	TREATMENT WITH INOSITOL ALONE BEGIN- NING DAY OF INFECTION AND CONTINUING 11 WEEKS, GROUP L
		Group A, 1 week	Group B, 2 weeks	Group C, 4 weeks	Group D, 11 weeks	Group F, 1 week	Group G, 2 weeks	Group H, 3 weeks	Group I, 4 weeks		
1	15	18	9	10	1	1	1	4	6	6	14
2	8	14	5	14	1	4	1	3	2	14	4
3	20	16	20	7	—	6	1	4	—	4	20
4	16	19	14	1	—	2	1	2	1	3	20
5	20	7	17	6	—	1	1	2	2	11	20
6	11	10	5	—	1	2	2	1	1	10	18
7	15	18	12	14	1	1	1	4	8	1	12
8	20	20	15	2	2	—	1	8	1	—	9
9	1	7	9	5	—	2	3	4	4	9	20
10	20	12	16	7	1	—	2	8	3	2	9
Average..	14.6	14.1	12.2	7.1	0.7	1.9	1.4	4.0	2.8	6.4	14.6

<sup>1</sup> At necropsy the amount of tuberculous involvement was noted in the omentum and lymph nodes, the spleen, the liver, the lungs and the peritoneum and kidneys; and each was rated on the basis of 0 to 4 according to the extent of involvement. The sum of these gives the "tuberculosis index" for each animal, and the sum of these divided by the number of animals gives the "average tuberculosis index" for the group. (See "The Action of Some Derivatives of 4-4' Diaminodiphenylsulfone in Experimental Tuberculosis" by M. I. Smith, E. W. Emmart and E. F. Stohlman, *Am. Rev. Tuberc.*, 1943, 48.)

<sup>2</sup> Died soon after infection.

invasiveness of the tubercle bacillus, the progress of the disease, or to prevent tissue destruction.<sup>3</sup>

<sup>3</sup> Since this has been written, another experiment has been carried out more recently with 10 controls and 10 guinea pigs treated with the nearly maximum tolerated dose of 50 mg/kg streptomycin twice daily for three weeks. Three of the treated guinea pigs died of drug toxicity at ten to twelve days. The experiment was terminated at one hundred five days. At this time 8 of the 10 controls had died and the average tuberculosis index for the whole group was 10.7. The seven survivors of the group treated with streptomycin for three weeks all had generalized tuberculosis with an average index of 6.7.

*Variation in the time interval between infection and beginning of treatment:* Eleven weeks of treatment with streptomycin started one to two weeks after infection (groups F and G), gave almost as good results in suppressing the disease as when treatment was begun the day of infection. The tuberculosis index in these two groups was 1.9 and 1.4, respectively, as compared with 14.6 in the controls (table 1). All the animals in these two groups survived (table 2). The average weight curves for these two groups were almost as good as for the group

TABLE 2

*The influence of duration of treatment with streptomycin and of the time interval between infection and beginning of treatment for groups of guinea pigs*

GROUP	TREATMENT	NUMBER OF ANIMALS IN GROUP	NUMBER OF ANIMALS WHICH DIED	PERCENT REACTORS IN RELATION TO SURVIVORS	TUBERCULOSIS INDEX <sup>1</sup>		PERCENT OF EACH GROUP FREE FROM LESIONS	AVERAGE CHANGE IN WEIGHT
					Range	Average		
E	Control	10	9	1/1	1-20	14.6	—	gm. -5.6
A	1 week, beginning day of infection	10	4	6/6	7-20	14.1	—	+96.8
B	2 weeks, beginning day of infection	10	2	7/8	5-20	12.2	—	+145.2
C	4 weeks, beginning day of infection	9	—	9/9	0-14	7.1	11	+278.9
D	11 weeks, beginning day of infection	10	—	7/10	0-2	0.7	40	+353.6
F	11 weeks, beginning 1 week after infection	10	—	10/10	0-7	1.9	20	+275.8
G	11 weeks, beginning 2 weeks after infection	10	—	8/10	0-3	1.4	—	+307.6
H	11 weeks, beginning 3 weeks after infection	10	5	5/5	1-8	4.0	—	+171.2
I	11 weeks, beginning 4 weeks after infection	10	1	9/9	0-9	2.8	10	+212.8
N	Same as group I plus 0.2 gm./kg. Inositol intramuscular daily	9	4	5/5	1-14	6.4	11	+243.5
L	Inositol only as in N, 11 weeks, beginning day of infection	10	8	2/2	4-20	14.6	—	+75.2

<sup>1</sup> At necropsy the amount of tuberculous involvement was noted in the omentum and lymph nodes, the spleen, the liver, the lungs and the peritoneum and kidneys; and each was rated on the basis of 0 to 4 according to the extent of involvement. The sum of these gives the "tuberculosis index" for each animal, and the sum of these divided by the number of animals gives the "average tuberculosis index" for the group. (See "The Action of Some Derivatives of 4-4' Diaminodiphenylsulfone in Experimental Tuberculosis" by M. I. Smith, E. W. Emmart and E. F. Stohlman, *Am. Rev. Tuberc.*, 1943, 48.)

treated from the day of infection (curves F, G and D, figure 2). Few of the animals in these two groups, however, were completely free from tuberculosis.

When treatment was delayed for three to four weeks after infection, as in groups H and I, the tuberculosis index was increased to 2.8 to 4.0 (table 1), the mortality rate appeared to be increased (table 2), and the average weight curves were reduced (H and I, figure 2). However, comparison of this series with the preceding series of 4 groups makes it appear that, from the standpoint of efficacy



of treatment, it is more important to make sure that the period of treatment is adequately long than to place excessive emphasis on avoiding delay in the beginning of treatment after infection (figures 3 and 4).

*Effect of inositol and its influence on streptomycin:* The action of daily injections of inositol in experimental tuberculosis, when treatment was begun the day of infection and continued for eleven weeks, is shown in group L, tables 1 and 2.

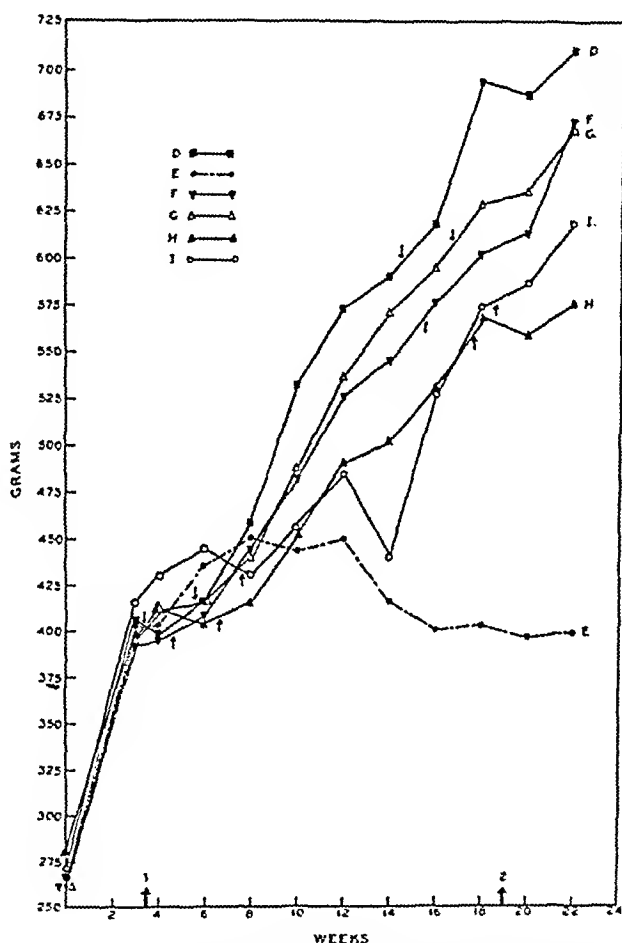


FIG. 1. Average weight curves of groups of tuberculous guinea pigs treated with 20 mg/kg streptomycin twice daily beginning on the day of infection: group A, one week; group B, two weeks; group C, four weeks and group D, eleven weeks; group E controls. First arrow indicates time of inoculation and beginning of treatment; second arrow time of PPD testing.

Comparison with the untreated controls of group E shows that inositol is without effect, the mortality rate in the inositol groups being 80 per cent as compared with 90 per cent for the controls, and the tuberculosis index 14.6, identical with that of the controls. The influence of inositol on the chemotherapeutic efficacy of streptomycin may be seen by comparing groups I and N, tables 1 and 2, figures 4 and 5. The mortality rate of I was 10 per cent as compared with 45 per cent

for N (table 2), and the tuberculosis index for I was 2.8 or less than one-half that of N, which was 6.4 (table 1 and figure 4). The average weight curves for groups I and N, in comparison with the untreated control group E and the group treated with inositol alone, L, is shown in figure 5. It appeared that under the experi-

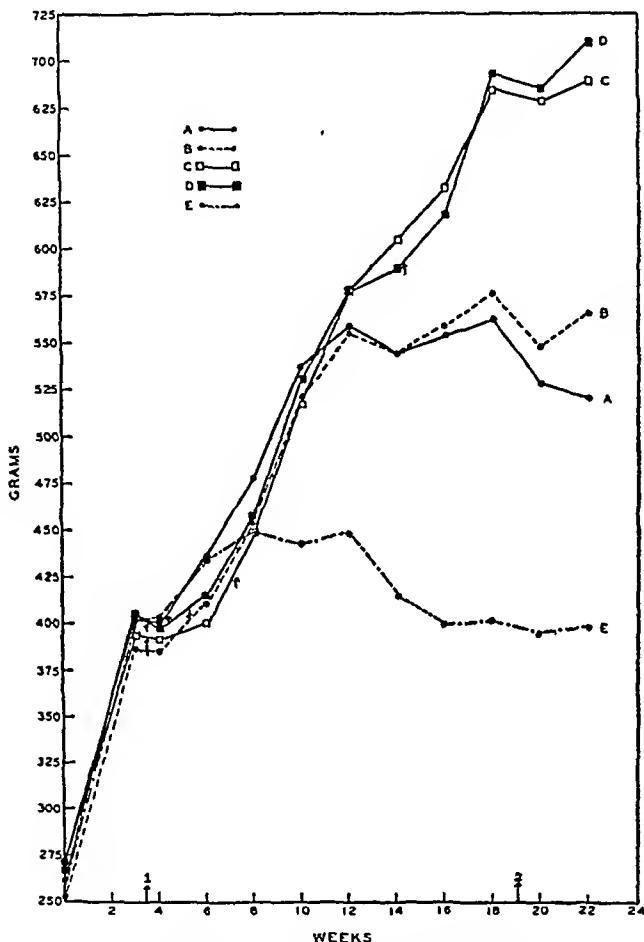


FIG. 2. Average weight curves of groups of tuberculous guinea pigs treated with streptomycin 20 mg/kg twice daily for eleven weeks with varying intervals between infection: group D treatment begun day of infection; group F, one week; group G, two weeks; group H, three weeks and group I, four weeks; group E, untreated controls. First arrow indicates time of infection, second, time of PPD testing. Small arrows on the curves indicate beginning and end of treatment.

mental conditions inositol had in some measure counteracted or nullified the chemotherapeutic efficacy of streptomycin.

#### DISCUSSION

The present experiments were undertaken to determine whether intensive treatment with streptomycin during the first month of infection would be suffi-

cient to protect guinea pigs from the destructive effects of *M. tuberculosis*. Acute tuberculosis infection in the guinea pig may be divided roughly into three phases: (a) the preinvasive state, the period of "freely growing bacilli" (7) during the first one to two weeks before the tubercle bacilli have established their intracellular parasitic existence; (b) the period of invasiveness, during the next one to two weeks following infection when rapid dissemination of the invading

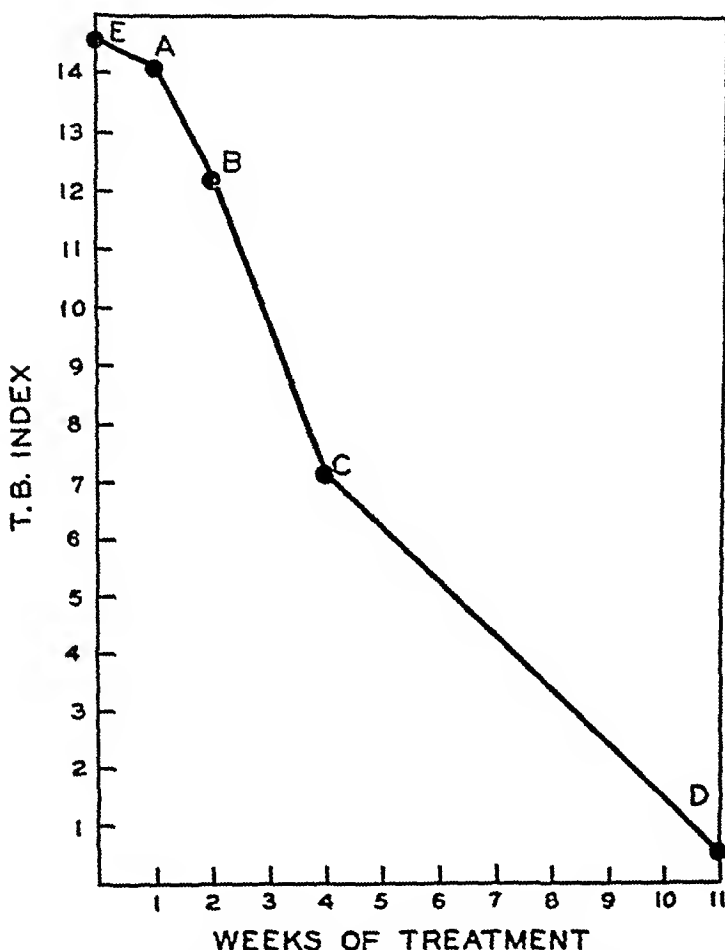


FIG. 3. Relation of duration of treatment with streptomycin and the extent of tuberculous involvement in groups of tuberculous guinea pigs: group A, treated one week; group B, two weeks, group C, four weeks, group D, eleven weeks, all treatment begun day of infection; group E, untreated controls.

microorganism occurs with tubercle formation in organs and tissues of predilection; and (c) the phase of tissue destruction, necrosis, and death of the host. The results of this study indicate that streptomycin has no chemotherapeutic efficacy when treatment is restricted to the first phase; little or no efficacy when treatment is restricted to the first and second phases; and that its greatest effectiveness is realized when treatment is applied throughout the three phases of infection. It

is significant that, when treatment was restricted to the third phase of the infection, the results were better than when applied during the first two phases and, in some cases, were almost as good as when treatment was applied throughout the entire course of infection. This suggests a possible mechanism of action of streptomycin. This greatest activity of streptomycin, at a phase of infection

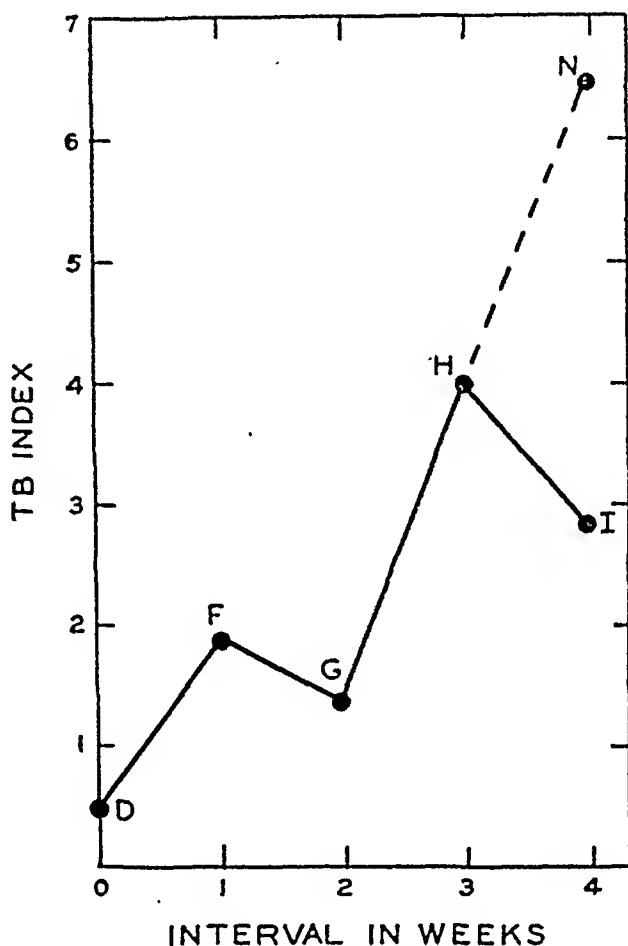


FIG. 4. Relation of time interval between infection and beginning of treatment and the extent of tuberculous involvement in groups of infected guinea pigs. Group D treatment begun day of infection; group F, one week after infection; group G, two weeks; group H, three weeks; group I, four weeks; group N treated as group I but in combination with inositol.

when the tubercle bacillus exerts its greatest destructive effect in the tissues of the untreated host, indicates that the chemotherapeutic action of the drug is best evolved during the peak of mutual interaction of the tissues of the invaded host and the invading microorganisms. An alternate explanation might be that streptomycin may detoxify or inactivate toxins liberated by *M. tuberculosis* which are destructive to the tissues of the host. The practical implication

of these findings is that it is advisable to apply intensive treatment with streptomycin as soon as is feasible, and to continue the treatment for an adequately long period of time. In the acute and subacute infections in guinea pigs, this period is ten to twelve weeks. What it should be in man must be determined by clinical trial.

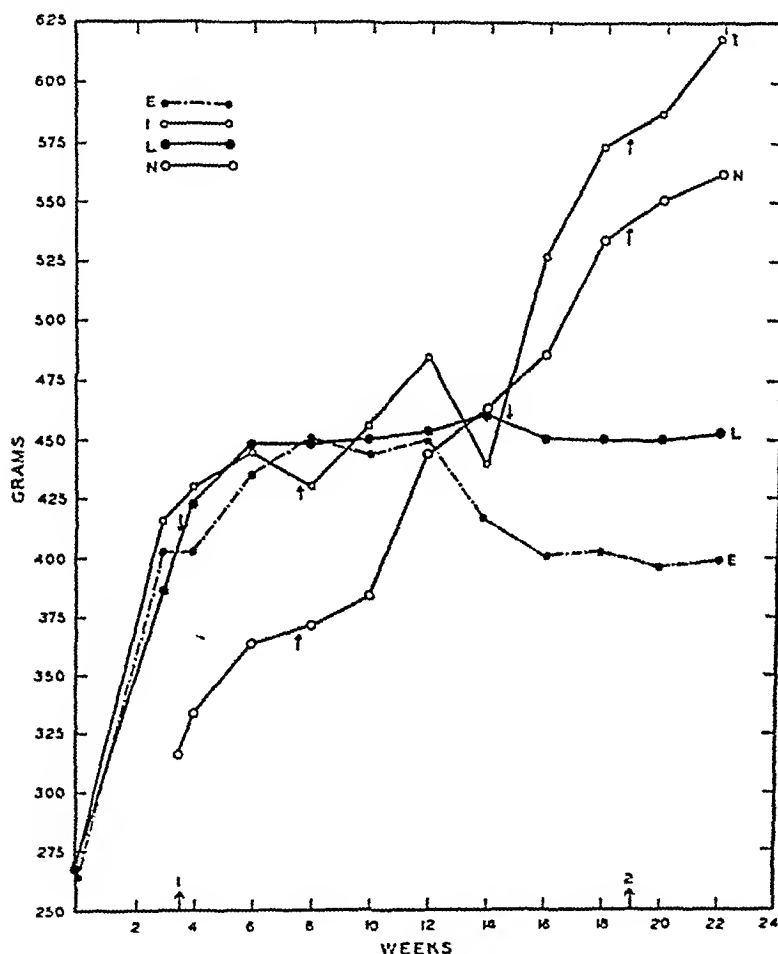


FIG. 5. Average weight curves of groups of tuberculous guinea pigs treated for eleven weeks with streptomycin (group I), streptomycin plus inositol (group N), treatment begun four weeks after infection. Group L treatment with inositol alone for the same length of time but treatment begun day of infection. Group E untreated controls. Arrow 1 indicates time of infection, arrow 2 time of PPD testing. Small arrows on the curves indicate beginning and end of treatment.

The experiments with inositol and streptomycin indicated that the chemotherapeutic action of the latter was inhibited by inositol. Inositol has been isolated from the phospholipids of *M. tuberculosis* (4). Theoretically, inositol could be synthesized from glycerol which is a nutrient for *M. tuberculosis*. Thus inositol may be an essential metabolite in the growth of tubercle bacilli. The

similarity in chemical structure of streptomycin and inositol suggests that the inhibiting action of streptomycin on *M. tuberculosis* may be another example of the antibacterial action of a chemical substance structurally related to an essential metabolite.

#### SUMMARY

Intensive treatment with streptomycin during the several phases of tuberculous infection in guinea pigs resulted in little evidence of chemotherapeutic activity when the treatment was restricted to the first four weeks of infection. This period coincides with the preinvasive period and the period of early invasiveness. A high degree of chemotherapeutic activity was observed when streptomycin was administered during the third stage of infection, which coincides with the period of generalized tissue destruction and necrosis.

Inositol has no effect on experimental tuberculosis infection in guinea pigs. Inositol appeared to antagonize the chemotherapeutic action of streptomycin when the two were used together. It is suggested that this antagonistic action may be another example of antibacterial action of a chemical analogue structurally related to an essential metabolite.

#### SUMARIO

##### *La Estreptomicina en la Tuberculosis Experimental del Cobayo*

(a) Efecto de la duración del tratamiento y del tiempo transcurrido entre la infección y el comienzo de la terapéutica.

(b) Influjo del inositol y su acción antagónica a la estreptomicina.

El tratamiento intenso con estreptomicina durante las varias fases de la infección tuberculosa en los cobayos indicó poca actividad quimioterapéutica si el tratamiento se limita a las primeras cuatro semanas de infección, que coinciden con el período preinvasor y el período de invasión temprana y mucha actividad si se aplica el tratamiento durante la tercer etapa de infección que coincide con el período de histólisis general y esfacelo.

El inositol no ejerció efecto alguno sobre la infección tuberculosa experimental en los cobayos, y aparentemente antagonizó la acción quimioterapéutica de la estreptomicina cuando se empleaban simultáneamente. Ese antagonismo puede constituir otro ejemplo de acción antibacteriana por un producto químico análogo, estructuralmente afín de un metabolito esencial.

#### *Addendum*

Since completion of this work, Rhymer and associates (9) have reported on the antistreptomycin activity of a brain extract which they identified as lipositol. Lipositol, according to Woolley (10), is an inositol-containing phospholipid, with 16 per cent inositol and 15.5 per cent galactose in its structure.

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# THE ACTION OF GASTRIC CONTENTS ON TUBERCLE BACILLI

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## INTRODUCTION

In a previous paper (1) it was shown that many specimens of gastric contents obtained by lavage are able to inhibit tubercle bacilli present, particularly if the specimens are kept at warm temperatures. The present paper is a more thorough investigation of this phenomenon.

In addition to the hydrochloric acid and pepsin present in most specimens of gastric contents, saliva and bile may also be found. Evidently one or all of these substances contribute to the inhibitory action the lavage material exhibits against tubercle bacilli.

Saliva contains inhibitory substances against *M. tuberculosis* as was demonstrated by Piasecka-Zeyland and Zeyland (2) and Dold and Ochsenreither (3). Other bacteria are also inhibited by saliva, as demonstrated by Dold and Weigman (4), Bibby, Hine and Clough (5), and Van Kesteren, Bibby, Berry and others (6). Bartle and Harkins (7) and Hurst (8) are among the many workers who have pointed out the strong bactericidal effect of acid. Pepsin has thus far not been found active against tubercle bacilli. Bile has been similarly vindicated by Floyd and Page (9). Whole gastric juice, either natural or artificial, has been shown to be harmful to tubercle bacilli by Lester (10), Floyd and Page (9), Schwarting (1), Kramer (11), and Sprick and Towey (12). In addition to the usual components of gastric juice, Ames, Culver and Nungester (13) have found a germicidal factor present in gastric lavages.

Tubercle bacilli must be exposed to gastric juice for at least ten hours before being seriously injured. Because of this fact, early workers have perhaps overlooked the harmful effect of lavage solutions. Delay caused by mailing specimens to public health laboratories may result in many falsely negative cultures. Furthermore, the practice of pooling several days' lavages and culturing the composite sample is unsound in the light of experimental evidence. In the writer's experience, inhibitory lavages kill all the contained tubercle bacilli if the delay is long enough for the temperature employed.

In order to determine the frequency and character of the inhibitory lavage, a survey of 50 gastric lavages was undertaken.

## METHODS

The following data were recorded for each specimen: (1) reaction to litmus or nitrazine papers; (2) presence and amount of pepsin. (Kleiner test) (14); and (3) number of tubercle bacilli present on smear of control.

All lavages were taken from the fasting stomach, using not more than 200 cc. of sterile distilled water in the process of collection. Four aliquots of 4 cc. each were measured into round-bottom 50 cc. centrifuge tubes. Each aliquot was seeded with an aqueous suspension of tubercle bacilli to produce a final concentration of .001 mg. of bacilli per cubic centimeter of lavage. This amount yielded sediment smears of Gaffky I or II.

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Immediately after seeding, portion No. 1 was treated by the Hanks, Clark and Feldman method (15) and the resulting sediment was planted on three tubes of Petragnani's medium. This portion acted as the control, and in all cases it produced heavy, confluent growth.

The remaining three aliquots were placed: at incubator temperature, 37° C, (portion No. 2); room temperature, (portion No. 3); and icebox temperature, (portion No. 4); and left until the following morning. At that time the aliquots were treated and planted as in the control portion. Cultures were observed twice weekly for six weeks. In summarizing the data from these cultures, the final, or twelfth, observation was used.

Lavages which showed no growth in the 37° C incubated portions were considered inhibitory and were graded according to the amounts of inhibition noted in the room and icebox portions. Those showing a few colonies in the warm incubated portion were considered doubtfully inhibitory. Specimens showing equal amounts of growth in all portions, regardless of the temperatures used, were noninhibitory.

TABLE 1

*Summary of cultural results after twenty-four hour exposure to gastric contents*

INHIBITORY ACTION	LAVAGES	
	Number	Per cent distribution
Total.....	50	100
Negative action.....	12	24
Inhibitory action.....	38	76
Doubtful.....	2	4
1 +.....	3	6
2 +.....	10	20
3 +.....	15	30
4 +.....	8	16

## RESULTS

The results of the survey are tabulated in table 1. It will be seen that 76 per cent of the lavages show some inhibitory power against tubercle bacilli. Twenty-four per cent lack this ability.

*Characteristics of Survey Lavages:* The 38 inhibitory lavages resembled one another in two respects. All were acid, and all contained some pepsin. Usually those with less acid contained the smaller amounts of pepsin, and the strongest inhibition was seen chiefly in the high-acid containing specimens.

Lavages showing no inhibition were sharply divided from the group above both as to pepsin and acid content. There were 12 noninhibitory lavages, only one of which was acid. Ten of the lavages were neutral in reaction, and one was alkaline (pH 7.5). Only 2 of the lavages contained pepsin. One lavage contained both acid and pepsin, but for some reason was noninhibitive.

Pepsin apparently played no part in the inhibitive process. Some of the non-inhibitive lavages contained pepsin but no acid, and in these cases the pepsin alone had no apparent effect on tubercle bacilli.

*Effect of Acid and Pepsin on Tubercle Bacilli:* As acid and pepsin in combination were most frequently found in specimens with inhibitive power, an artificial

gastric juice was prepared according to Floyd and Page (9) to test the properties of these two components. Composite results are presented in table 2.

The formula for gastric juice derived from Floyd and Page contained acid and pepsin contents corresponding to normal stomach values. The tests described in table 2 were performed as in the survey previously described. Several trials of each combination were recorded, and a composite result taken for the table. All control portions yielded 4+ growth.

The artificial gastric juice was less potent than natural secretions. An inconsistency was noted in that acid alone was more strongly inhibitive than the entire gastric juice formula. Differences between artificial gastric juice and natural secretions are perhaps explained by the presence of germicidal factors in saliva or bile, or by unknown substances in the cellular elements.

By neutralizing the natural lavages to remove the effect of the acid, it was hoped that the residual inhibitive effect might be demonstrated when tested against small amounts of tubercle bacilli. Unfortunately, these experiments

TABLE 2  
*Effect of acid and pepsin on tubercle bacilli*

COMPOSITION	GROWTH	INHIBITORY ACTION
Pepsin—no acid.....	4 +	Negative
Acid—no pepsin.....	Negative	2 +
Pepsin and acid.....	1 to 7 c*	Doubtful
Pepsin plus acid, boiled to destroy pepsin before seeding.....	Negative	2 +
Pepsin plus acid, neutralized to prevent action of both pepsin and acid before seeding.....	4 +	Negative

\* c = colonies.

were inconclusive, as acid evidently accounts for the majority of the inhibitive property.

*Natural Gastric Lavages:* In all of the foregoing experiments, large amounts of tubercle bacilli were present to act as an indicator of inhibition. Despite the heavy seeding, many of the lavages were sufficiently inhibitory to kill off all the organisms present, especially at the warmer temperatures. If such a strongly inhibitive specimen contained a very small number of bacilli, it is likely that all organisms would perish if the specimen were subjected to delay or exposure to warm room temperatures before being treated for culture.

As this question is of importance to public health laboratories or other central laboratories, which depend on the mails for receipt of specimens, a series of 18 naturally positive lavages was studied. As before, the lavages were divided into aliquots, but only 3 were used.

Portion No. 1 was digested immediately and cultured. Portions No. 2 and No. 3 were held at room and icebox temperatures for forty-eight hours respectively before being digested and cultured. It was believed that the lower

temperatures and longer delays would simulate conditions met in actual practice.

As a result of the small numbers of bacilli present, errors of sampling and distribution complicate the determinations. Therefore, wherever the control portions were negative, the grade of inhibition was undetermined. Likewise, those specimens which yielded only one or two colonies in the tested portions were considered doubtful. Only those lavages which contained a fair number of colonies in the control portion were assigned definite inhibition grades. The summary of this series may be seen in table 3.

In this series, 10 of the 18 lavages were positive for tubercle bacilli when cultured immediately. When held forty-eight hours in the icebox before being

TABLE 3

*Results of temperature and the inhibitory action on naturally positive lavages*

NUMBER	SMEAR	IMMEDIATELY CULTURED	ROOM TEMPERATURE (48 HOURS)	ICE BOX TEMPERATURE (48 HOURS)	INHIBITORY ACTION
1	G 1	43 c <sup>1</sup>	56 c*	23 c*	Negative
2	G 3	4 +	Negative	25 c*	Positive
3	Negative	2 c*	Negative	1 c*	Doubtful
4	Negative	1 c*	Negative	Negative	Doubtful
5	Negative	22 c*	Negative	Negative	Positive
6	Negative	1 c*	Negative	Negative	Doubtful
7	Negative	Negative	Negative	Negative	Undetermined
8	Negative	Negative	Negative	Negative	Undetermined
9	G 2	4 +	4 +	4 +	Negative
10	G 2 <sup>2</sup>	Negative	Negative	Negative	Undetermined
11	Negative	56 c*	Negative	Negative	Positive
12	G 2	3 +	Negative	Negative	Positive
13	Negative	21 c*	Negative	Negative	Positive
14	Negative	Negative	Negative	Negative	Undetermined
15	Negative	Negative	Negative	1 c*	Doubtful
16	Negative	Negative	Negative	Negative	Undetermined
17	Negative	Negative	Negative	Negative	Undetermined
18	Negative	Contaminated	Negative	1 c*	Doubtful

<sup>1</sup> Partially contaminated with nonacid-fast bacteria.

<sup>2</sup> Atypical acid-fast bacilli.

\* c = colonies.

digested and cultured, only 6 of the 10 lavages remained positive. After being held forty-eight hours at room temperature before being digested and cultured, only 2 of the lavages remained positive. Thus, a delay of forty-eight hours at room temperature considerably reduced the number of positive lavages.

#### DISCUSSION

From these data it appears that approximately three-fourths of adult gastric lavages are harmful to tubercle bacilli. Delay, especially at warmer temperatures, permits inhibitory lavages to kill off many of the bacilli, thus producing false negative cultures.

The best cultural results are obtained if lavage specimens are digested and cultured as soon after collection as possible. Pooling lavages for days before culturing the composite sample seems unjustified.

## SUMMARY

1. In a series of 50 seeded gastric lavages, 38, or 76 per cent, were bactericidal for tubercle bacilli.
2. Inhibitory lavages were acid and usually contained some pepsin.
3. Natural gastric lavages, which may contain bile, saliva, cellular elements and germicidal factors, are more strongly inhibitory than artificial gastric juices.
4. The bactericidal effect of gastric lavages is directly related to the length of time and the height of temperature at which the lavages are kept.

## SUMARIO

*Acción del Contenido Gástrico sobre el Bacilo Tuberculoso*

1. En una serie de 50 lavados gástricos sembrados, 38, o sea 76 por ciento, mostráronse bactericidas para los bacilos tuberculosos.
2. Los lavados inhibidores eran ácidos y contenían por lo general pepsina.
3. Los lavados gástricos naturales, que pueden contener bilis, saliva, elementos celulares y factores germicidas, son inhibidores más poderosos que los jugos gástricos artificiales.
4. El efecto bactericida de los líquidos de lavado gástrico guarda relación directa con el tiempo y la temperatura a que se guardan.

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# THE SUBEFFECTIVE DOSE OF STREPTOMYCIN IN EXPERIMENTAL TUBERCULOSIS OF GUINEA PIGS<sup>1</sup>

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In studies of the effect of using two or more chemotherapeutic agents together in an experimental infection, it is necessary that the dose of each drug be low enough so that one of the drugs alone will not be responsible for the maximal therapeutic response. If the dose of one drug in a combination is great enough to result in a reversal of a progressive disease and healing of the lesions equal to that produced by the combined treatment, it will not be possible to conclude anything about the beneficial effects of the combination.

In experimental tuberculosis of guinea pigs, it has been demonstrated that 6 mg. of streptomycin daily will exert a strikingly favorable effect on the disease when treatment is continued for one hundred and sixty-six days, starting forty-nine days after inoculation with 0.001 mg. of virulent human type tubercle bacilli (1). It has also been shown that 6 mg. of streptomycin daily will arrest the progress of the disease in guinea pigs when treatment is continued for only fifty-four days, even when the beginning of treatment is delayed for twenty-one days after inoculation with 0.1 mg. of bovine or freshly isolated human type tubercle bacilli (2). Moreover, it has been observed that the favorable effect of treating tuberculous guinea pigs with 6 mg. of streptomycin daily may occur as soon as twenty-one days, even when treatment has been delayed for three weeks after inoculation with 0.1 mg. of virulent human type of tubercle bacilli.

When studies on the effect of combining streptomycin therapy with other chemotherapeutic agents in experimental tuberculosis were anticipated, it was necessary to find the dose of streptomycin that would result in a response less favorable than that obtained with a daily dose of 6 mg. of the drug.

## METHODS

Fifty-eight mature male guinea pigs, each weighing 500 to 600 gm., were each inoculated subcutaneously over the sternum with 0.1 mg. (moist weight) of virulent human tubercle bacilli (H37Rv). Twenty days later, one animal died from unknown causes, but was found to have visible miliary tubercles in the spleen and liver. On the twenty-first day, 4 guinea pigs were killed; each had lesions of tuberculosis in the lungs, liver and spleen. The remaining 53 animals were divided into seven groups, as shown in table 1. The various daily doses of streptomycin<sup>2</sup> were made by dissolving the drug in sterile water in concentrations of 20.0, 6.0, 4.0, 2.0, 0.5 and 0.1 mg. per mil., respectively. The individual doses were injected twice daily in 0.5 mil. amounts subcutaneously in the axillary space. One group of animals served as untreated controls. Treatment was continued for fifty-six days, at the end of which time all the animals were killed. Portions of tissue were selected for subsequent histologic examination.

In a second experiment, 60 male guinea pigs, the average weight of which was slightly more than 500 gm., were each inoculated subcutaneously over the sternum with 0.001

<sup>1</sup> Division of Experimental Medicine, Mayo Foundation, Rochester, Minnesota.

<sup>2</sup> The streptomycin used in these studies was furnished through the courtesy of the late Doctor Robertson, Merck & Co., Rahway, New Jersey.

mg. (moist weight) of H37Rv. Ten animals died between the thirty-fifth and the forty-second day after infection, all had visible lesions of advanced tuberculosis. On the forty-second day of infection, the surviving animals were divided into three groups as shown in table 2. Several animals of each group died soon after treatment was started and are not included in the table.<sup>3</sup> Nine animals were treated daily with 6 mg. of streptomycin given in two daily injections of 0.5 mil. of a solution containing 6 mg. of the drug per mil. Eleven animals received only 2 mg. of streptomycin daily given in two daily injections of

TABLE 1

*Average severity of tuberculosis expressed numerically based on histopathologic characteristics\* (S) (experiment 1)*

STREPTOMYCIN	ANIMALS	SPLEEN (MAX.: 35)	LUNGS (MAX.: 30)	LIVER (MAX.: 25)	SITE OF INOCULATION (MAX.: 10)	AVERAGE INDEX OF INFECTION (MAX.: 100)
<i>mg. per day</i>						
20.0	8	0.25	0.37	0.75	1.2	2.57
6.0	8†	4.9	4.9	0.25	3.2	13.2
4.0	8	0.5	0.9	0.5	0.0	1.9
2.0	8	20.0	5.2	2.5	2.5	30.2
0.5	8	30.7	13.2	15.2	8.7	67.8
0.1	7	33.0	6.3	18.4	10.0	67.7
Control	6	32.5	21.6	25.0	8.3	87.4

\* Treatment started twenty-one days after inoculation and continued for fifty-six days.

† Three animals in this group were treated for only twenty-four, twenty-eight and thirty days, respectively.

TABLE 2

*Average severity of tuberculosis expressed numerically based on histopathologic characteristics\* (experiment 2)*

STREPTOMYCIN	ANIMALS	SPLEEN (MAX.: 35)	LUNGS (MAX.: 30)	LIVER (MAX.: 25)	SITE OF INOCULATION (MAX.: 10)	AVERAGE INDEX OF INFECTION (MAX.: 100)
<i>mg. per day</i>						
6.0	9	1.2	1.6	0.7	3.3	6.8
2.0	11	20.0	4.7	9.2	7.3	34.2
Control	12	35.0	21.0	21.7	9.1	86.8

\* Treatment started forty-two days after subcutaneous inoculation with 0.001 mg. of virulent human tubercle bacilli.

0.5 mil. of a solution containing 2 mg. per mil. There were 12 untreated controls. Treatment was continued for one hundred and nineteen days, at the end of which time all the survivors were killed. Many of the animals in each group died before the end of the experiment,<sup>4</sup> but among the treated groups the duration of therapy was comparable; fifty days for the 6 mg. group, fifty-one for the 2 mg. group. The average duration of life of the control animals was fifty-eight days beyond the time when therapy was started in the two treated groups.

<sup>3</sup> In all studies on the chemotherapy of experimental tuberculosis in this laboratory, animals which die before completing twenty-one days of treatment are considered as "failures."

<sup>4</sup> The virus of lymphocytic choriomeningitis was identified by our associates, Dr. Heilman and Dr. Weed, in the tissues of several animals that died in both of these experiments.

## RESULTS

The average severity of the disease, as determined by histopathologic characteristics (3), in each group of the first experiment is given in table 1. Three animals of the group treated with 6 mg. of streptomycin daily died after only twenty-four, twenty-eight and thirty days of treatment, respectively. In these 3 animals, there was microscopic evidence of regression and healing of pulmonary and hepatic lesions, but the activity of lesions in the spleen and at the site of inoculation was sufficient to account for the higher average index of infection of the entire group. Excluding the active lesions in these animals, which were treated for only a short time, it was apparent that daily treatment with 20 mg., 6 mg., or 4 mg., of streptomycin for fifty-six days resulted in a marked diminution of the progressive tuberculosis that was present when treatment was started. There was no gross or microscopic evidence that the daily treatment with 6 mg. or 20 mg. was more beneficial than treatment with 4 mg. With all three doses there was a marked regressive change to a nonprogressive healing process. In tissues from animals that received only 2 mg. of streptomycin daily, the favorable effect was much less pronounced, although there was microscopic evidence of an attempt to restrict the disease by fibrosis in the liver and lungs. In many of these animals there were active lesions in the spleen, but they were less extensive than in the untreated controls. Streptomycin in doses of 0.5 or 0.1 mg. daily had little effect in changing the microscopic appearance of the disease from one of an advancing process to that of a restricted nonprogressive lesion.

The histologic findings in the second experiment (table 2) revealed that the daily dose of 2 mg. of streptomycin resulted in an incomplete regression of the disease as compared to the marked diminution of the lesions in the animals which received 6 mg. daily. In the latter group, the lesions in the spleen, liver, and lungs were definitely inactive and fibrotic. Many of the spleens contained calcified foci. The lungs and liver of the guinea pigs that received 2 mg. daily also showed many inactive healing lesions as compared to the controls, but active tubercles with a minimum of fibrosis were present in the spleens.

## SUMMARY AND CONCLUSIONS

In order to study the effect of combining streptomycin therapy with other agents in tuberculosis of guinea pigs, it was necessary to find the dose of streptomycin which would result in only a partial reversal of the disease process so that any effect of added drugs could be detected. Guinea pigs were infected with 0.1 mg. of virulent human tubercle bacilli and twenty-one days later were divided into seven groups. The animals in six groups were each treated daily with 20.0, 6.0, 4.0, 2.0, 0.5 and 0.1 mg. of streptomycin, respectively, for fifty-six days and one group served as controls. Histologic examination of the lungs, liver, spleen, and site of inoculation revealed that daily injections of streptomycin in doses of 20.0, 6.0 and 4.0 mg. were equally effective in changing the advancing unrestricted disease dramatically to a nonprogressive one. There was no microscopic evidence that daily injections of 20.0 or 6.0 mg. were more beneficial than injections of 4.0 mg. The use of 2.0 mg. daily resulted in only an incomplete change of the progressive disease. There were residual foci of activity in the



spleens of most of these animals in contrast to the absence of active lesions in those treated with larger doses.

In a second experiment, daily treatment of two groups with 6.0 and 2.0 mg., respectively, was started forty-two days after infection with 0.001 mg. of tubercle bacilli. The average duration of treatment was fifty and fifty-one days, respectively. In this, as in the first experiment, the daily administration of 6.0 mg. of streptomycin resulted in microscopic evidences of repair and healing. There were no active tuberculous lesions in the liver, spleen, or lungs of any of the animals. In those that received 2.0 mg. of streptomycin daily, there were active foci in the spleens of all but 3. Lesions in the lungs and liver were much less extensive than in the untreated controls, but the degree of fibrosis and diminution of the disease was less than in those given 6.0 mg. daily.

It is concluded that a daily dose of streptomycin of 2.0 mg. will be only partially effective in experimental tuberculosis of guinea pigs and may be used as the subeffective dose in testing the additive effect of other drugs in combination with streptomycin therapy.

#### SUMARIO Y CONCLUSIONES

##### *La Dosis Subefectiva de Estreptomicina en la Tuberculosis Experimental del Cobayo*

A fin de estudiar el efecto de la estreptomicinoterapia combinada con otros agentes en la tuberculosis del cobayo, resultó necesario descubrir la dosis de estreptomicina que no obtendría más que una reversión parcial del proceso patológico, permitiendo así observar el efecto, si lo hubiere, de las drogas agregadas. Se infectó a cobayos con 0.1 mg. de bacilos tuberculosos humanos virulentos, dividiéndoseles 21 días después en siete grupos. Los animales pertenecientes a seis grupos fueron tratados a diario con 20.0, 6.0, 4.0, 2.0, 0.5 y 0.1 mg. de estreptomicina, respectivamente, durante 56 días, sirviendo el otro grupo de testigo. El examen histológico de los pulmones, hígado, bazo y sitio de inoculación reveló que las inyecciones diarias de estreptomicina a dosis de 20.0, 6.0 y 4.0 mg. eran igualmente eficientes para cambiar dramáticamente la enfermedad de ilimitada y en vías de agravación a no progresiva. No hubo datos microscópicos de que las inyecciones diarias de 20.0 ó 6.0 mg. fueran más beneficiosas que las de 4.0 mg. El empleo de 2.0 mg. diarios sólo obtuvo una alteración incompleta de la fase progresiva, encontrándose focos residuales de actividad en los bazos de la mayor parte de los animales así tratados en contraposición a la falta de lesiones activas en los tratados con dosis mayores.

En el segundo experimento, se inició el tratamiento diario de dos grupos con 6.0 y 2.0 mg., respectivamente, a los 42 días de infectárseles con 0.001 mg. de bacilos tuberculosos. La duración media del tratamiento fué de 50 y 51 días, respectivamente. En este experimento, lo mismo que en el primero, la administración diaria de 6.0 mg. de estreptomicina dió por resultado signos microscópicos de regeneración y cicatrización, sin que se observaran lesiones tuberculosas activas en el hígado, bazo o pulmones de ninguno de los animales. En

los que recibieron 2.0 mg. diarios de estreptomycin, había focos activos en el bazo de todos los animales, menos 3. Las lesiones pulmonares y hepáticas fueron mucho menos extensas que en los testigos no tratados, pero la fibrosis y atenuación de la enfermedad fueron menores que en los que recibieron 6.0 mg. diarios.

Dedúcese que una dosis diaria de 2 mg. de estreptomycin sólo resultará parcialmente eficaz en la tuberculosis experimental del cobayo y puede usarse como dosis subefectiva al comprobar el efecto aditivo de otras drogas combinadas con la estreptomycinoterapia.

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## EDITORIAL

### Pneumoperitoneum

In 1946 Pinner<sup>1</sup> stated that there is no other treatment for pulmonary tuberculosis in which competent opinions are so far apart as in the indications for pneumoperitoneum. The intervening years and the introduction of a new treatment, streptomycin, into the picture have not altered the validity of his statement. This great divergence of opinion regarding the indications, effectiveness, and usefulness of pneumoperitoneum continues to exist in spite of the fact that well over a decade has passed since the procedure was first recommended by Banyai<sup>2</sup> and since a number of sanatoriums and clinics began to use pneumoperitoneum in selected cases.

Morriss<sup>3</sup> has remarked that the clinical course of a new treatment for tuberculosis is often characterized by a slow onset, when recognition and utilization are scant, a florid middle period of great enthusiasm, and a later period of partial disappointment and destructive criticism. There is increasing evidence that pneumoperitoneum is now rapidly entering the florid middle phase. Until now it has been extremely difficult to judge to what extent this sporadic but spreading enthusiasm for pneumoperitoneum is justified. Reports on large groups of treated cases were few, and follow-up was generally too brief to permit mature judgment.

Recently, several publications (notably the report of Mitchell, Hiatt, McCain, Easom, and Thomas,<sup>4</sup> and the very recent report of Trimble, Eaton, Crenshaw and Gourley<sup>5</sup>) have added greatly to the number of cases on which data are available. In the report of Trimble and his associates particularly, some fairly long term results have been tabulated. Even in this report, however, one may infer from the tables (though this is not specifically stated) that only approximately half the cases had been followed for more than two years after the institution of treatment. Presumably the average period of observation after arrest of tuberculosis in favorable cases was considerably shorter. Moreover, of the patients who had had disease arrested and pneumoperitoneum voluntarily discontinued, only 6 had subsequently been followed for more than two years. Informative and valuable as they are, even careful reports such as these will undoubtedly leave the skeptic considerably short of any final convictions regarding the proper place of pneumoperitoneum in modern tuberculosis therapy. It is high time, nevertheless, that every tuberculosis therapist face the need for a tentative appraisal of the procedure.

It can scarcely be denied that pneumoperitoneum is capable of favorably influencing the course of disease in certain patients. Like Trimble, I know of no

<sup>1</sup> *Am. Rev. Tuberc.*, 1946, 54, 589.

<sup>2</sup> *Am. J. M. Sc.*, 1931, 182, 360.

<sup>3</sup> *Am. Rev. Tuberc.*, 1942, 45, 623.

<sup>4</sup> *Am. Rev. Tuberc.*, 1947, 55, 303.

<sup>5</sup> *Am. Rev. Tuberc.*, 1948, 57, 433.

instance in which a physician has used pneumoperitoneum adequately on enough patients for a sufficient period of time and has then discarded it as a procedure of no value. The advantages of pneumoperitoneum, especially as compared to therapeutic pneumothorax, have been listed by too many writers to require repetition here. There is no longer reason to doubt that, in competent hands, pneumoperitoneum is a relatively safe procedure and that serious complications are relatively few. Moreover, a logical rationale for its use can be constructed, not merely from roentgenographic and fluoroscopic observations regarding the affected diaphragms of patients, but also from lung volume studies recently made by Wright<sup>6</sup> and quoted, in part, by Hiatt and Mitchell.<sup>7</sup>

Wright has made several extremely pertinent observations:

1. The degree of relaxation of pulmonary tissue produced by a given therapeutic procedure is best determined by studying the effect of the procedure upon the lung volume at mid-capacity, i.e., the air content of the lungs at the end of an ordinary quiet expiration. It is this volume, not the volume at the end of forced inspiration or expiration, which most accurately indicates the usual volumetric status of a patient's lungs during the twenty-four hours of the day. (Trimble has similarly pointed out the importance of studying the relative position and mobility of the diaphragms fluoroscopically during quiet respiration if the relaxing effect of pneumoperitoneum is to be estimated radiologically. This effect cannot be accurately estimated merely from conventional roentgenograms made on deep inspiration.)

2. When a patient, with or without pneumoperitoneum, changes from the erect to the recumbent position, lung volume at mid-capacity is reduced by 25 to 50 per cent.

3. In the study of a limited number of cases, Wright found that the effect of pneumoperitoneum without phrenic paralysis varied considerably and was sometimes extremely slight. In general, however, volume at mid-capacity in both the erect and recumbent position was reduced by 15 to 40 per cent from that measured with the patient in a corresponding position prior to pneumoperitoneum.

4. Observations on patients with phrenic paralysis and pneumoperitoneum were too limited to justify generalizations. In 2 patients with pneumoperitoneum, the addition of phrenic paralysis further decreased volume at mid-capacity to a marked degree (50 per cent over the expected levels in both positions).

5. In the cases studied, pneumoperitoneum produced little reduction in maximum breathing capacity (not over 10 per cent).

It may still be debated whether or not relaxation of diseased tissue is the principal factor responsible for the beneficial effects of collapse therapy in pulmonary tuberculosis. It is a commonly accepted theory that relaxation is, at least, a desirable therapeutic objective, and this theory has much evidence to support it. Wright's studies show that relaxation can usually be achieved by pneumoperitoneum, and both clinical and physiological observations indicate

<sup>6</sup> Unpublished data of Dr. George W. Wright, Trudeau, New York. These data are discussed here by the kind permission of Dr. Wright.

<sup>7</sup> North Carolina M. J., 1947, 8, 710.

that pneumoperitoneum is less likely than pneumothorax to produce serious impairment of ventilatory function. Reasons for the suggestion, made by Banyai,<sup>1</sup> that a patient be treated in a semi-recumbent position for maximum pneumoperitoneum effect were never clear or logical. Wright has now made it apparent that maximum pulmonary relaxation is obtained from pneumoperitoneum when the patient is placed in the recumbent position.

To say that pneumoperitoneum is a useful therapeutic tool is easy; to resolve conflicting opinions and claims beyond this point is difficult.

It is not yet clear, for example, to what extent pneumoperitoneum should be used alone, to what extent it should be used in combination with phrenic paralysis. At the Laurel Heights Sanatorium, it has been our policy since 1937 to employ pneumoperitoneum almost exclusively as a supplement to phrenic paralysis in carefully selected patients. This policy was based on the observation, in patients with phrenic paralysis, that the addition of pneumoperitoneum almost never affected the position of the unparalyzed diaphragm as observed in conventional roentgenograms, while the paralyzed diaphragm usually rose to a position distinctly higher than that observed after phrenic paralysis alone. Sometimes the additional elevation was very marked. I am now convinced that the observations which led us to restrict the use of pneumoperitoneum to patients with phrenic paralysis were inadequate. Mitchell *et al.* have pointed out that a paralyzed diaphragm, being more readily affected, tends to limit the action of pneumoperitoneum to that side. Evidence that pneumoperitoneum alone can produce significant relaxation of lung has already been mentioned. Certainly one must view with concern reports that the combination of phrenic paralysis and pneumoperitoneum is likely to produce an excessive incidence of permanent diaphragmatic paralysis. Experience regarding this hazard is not the same in all clinics, however, and there can be no doubt that phrenic paralysis plus pneumoperitoneum will usually produce a considerably greater degree of relaxation or collapse of the affected lung than pneumoperitoneum alone. Pneumoperitoneum alone may suffice for many lesions; it can be employed at times when tuberculosis is sufficiently extensive bilaterally to make phrenic paralysis undesirable. Nevertheless, when the principal disease being attacked by pneumoperitoneum is unilateral, it seems only reasonable to employ both phrenic paralysis and pneumoperitoneum if the disease is severe or if pneumoperitoneum alone has already failed completely to arrest it.

Having conceded pneumoperitoneum its virtues, one still has reason to doubt that it has yet established its claim to such extensive and enthusiastic use as is now being accorded it in certain sanatoriums and clinics. In some centers the use of pneumoperitoneum has steadily increased until as many as one-third or even one-half of all patients now receive it. At the Laurel Heights Sanatorium, a ten year experience with pneumoperitoneum has led to a far more restricted use. Our use of pneumoperitoneum may, indeed, be much too limited. Nevertheless, those of us who still retain a conservative attitude toward pneumoperitoneum may point to certain reasons other than a mere reluctance to accept the new.

<sup>1</sup> Dis. of Chest, 1941, 7, 492.

The chief danger of pneumoperitoneum lies not in the procedure as such. The chief danger lies in the risk that the relative ease and safety of pneumoperitoneum and the readiness with which it is tolerated by most patients may lead to excessive and indiscriminate use. As the indications for pneumoperitoneum are broadened to include extensive disease of long standing on the one hand, milder and more susceptible lesions on the other, pneumoperitoneum comes increasingly in competition with other more time-tested forms of therapy. It should displace them only if its superiority is clear. I vigorously question, for example, the wisdom of using pneumoperitoneum for acute exudative minimal lesions largely for the purpose (as suggested by Trimble *et al.*) of curtailing treatment by bed-rest to approximately two months. Furthermore, results of pneumoperitoneum are relatively poor in patients with old fibrocascous and fibrocavernous lesions. Therefore, unless the patient is a poor surgical risk, it is obviously unwise to elect pneumoperitoneum for such lesions merely in the hope of avoiding an immediately more formidable, but ultimately more effective and more durable, thoracoplasty. Even in this era, with its vogue for looking askance at pneumothorax, one may often prefer it to pneumoperitoneum in suitable cases. True, the complications of pneumothorax are more numerous. In our own experience, however, an anatomically good pneumothorax, free of adhesions, is generally more reliable than pneumoperitoneum for the closure of cavities, the conversion of sputum, and the arrest of tuberculosis. Some of us still place these objectives above the avoidance of complications as criteria for successful therapy.

What, then, shall be our tentative appraisal of pneumoperitoneum at this time? This is bound to be a somewhat personal matter, influenced, in part, by one's own case material and experience, and by the attitudes, preferences and special skills of the surgeon with whom one works. The following tentative appraisal is the one I have reached.

Pneumoperitoneum is a useful and valuable therapeutic procedure, which is relatively safe and which can be well tolerated by most patients. It can often be successfully applied when bed-rest alone is inadequate and when pneumothorax and thoracoplasty are not well suited to the problem. When not completely successful, pneumoperitoneum can usually be abandoned without impairing the patient's suitability for an alternative procedure. An anatomically satisfactory pneumothorax or a thoracoplasty is, however, generally preferable to pneumoperitoneum when there is a good indication for one or the other of these procedures, and when the risks involved are not excessive.

Pneumoperitoneum is especially valuable in patients with active and progressive exudative or caseous pneumonic tuberculosis, who are too ill for thoracoplasty and in whom the risk of pneumothorax complications is high. Pneumoperitoneum will often produce sufficient improvement to bring such patients successfully to thoracoplasty even when it is inadequate, alone, to produce arrest of disease. Pneumoperitoneum also deserves a trial, oftentimes, following unsuccessful pneumothorax, provided that the extent of disease and the severity of pulmonary damage is limited, so that one is reluctant to proceed immediately to thoracoplasty. In both these situations, pneumoperitoneum is much more

likely to prove effective if the distribution of disease is such as to warrant the combination of phrenic paralysis with the pneumoperitoneum.

The value of pneumoperitoneum is limited in patients with extensive old fibrocaseous or fibrocavernous tuberculosis. This is also true when tuberculous bronchitis with bronchostenosis or tuberculous bronchiectasis is prominent. In such patients, either permanent collapse by thoracoplasty or pulmonary resection is usually preferable. When disease of these types is bilateral, so that thoracoplasty or resection is not feasible, one can scarcely raise a strong objection to a trial of pneumoperitoneum. Clinical improvement is, apparently, often observed. It can hardly be expected, however, that pneumoperitoneum will frequently produce complete and sustained arrest of tuberculosis in such patients.

Bed-rest remains the basic treatment for tuberculosis; pneumoperitoneum should be used in addition to bed-rest, not instead of it. There would be good reason for this statement even if relaxation of diseased pulmonary tissue were the sole advantage. The studies of Wright indicate that recumbency usually affects lung volume more consistently and to a greater degree than pneumoperitoneum does. The effects are additive, however, and a patient with pneumoperitoneum will obtain maximum relaxation of lung tissue when he is also recumbent.

KIRBY S. HOWLETT, JR.

# TREATMENT OF TUBERCULOSIS WITH STREPTOMYCIN<sup>1,2,3</sup>

Response of Certain Subacute and Chronic Types

KIRBY S. HOWLETT, JR., AND JOHN B. O'CONNOR

## INTRODUCTION

In November, 1946, a study of streptomycin in clinical tuberculosis was launched at the Laurel Heights Sanatorium. At that time evidence was already available from several sources (notably the pioneer work of Hinshaw and his associates (1, 2, 3, 4, 5, 6), the later work of McDermott *et al.* (2, 7), and the early cases observed from the joint streptomycin project of the Army, Navy, and Veterans Administration (8, 9) which strongly suggested that streptomycin did exert a suppressive and beneficial effect upon certain types of tuberculosis. In patients with pulmonary tuberculosis, the lesions most favorably affected appeared to be acute exudative tuberculosis of recent origin and ulcerative lesions of the respiratory tract. In general, the tendency of investigators at that time was to emphasize strongly the importance of the fresh exudative component in determining the suitability of patients with pulmonary tuberculosis for streptomycin treatment.

Certainly this emphasis seemed well placed, and patients with fresh exudative disease were included in the Laurel Heights study whenever suitable cases were found. The results observed in such cases closely paralleled the reported results of others. It was apparent from the beginning, however, that the number of patients with tuberculosis predominantly of the acute exudative type was limited in this institution, and it was further apparent that a considerable mass of information on the effects of streptomycin in such cases would soon be available from other sources.

Accordingly a decision was made to explore the action of streptomycin in certain types of tuberculosis which were not of recent origin and to include in the study patients with distinctly chronic disease, provided it was of a type which was believed to be still potentially reversible.

A few points should be immediately clarified before action of the streptomycin against the particular types of subacute and chronic tuberculosis which have especially interested the investigators is discussed. The first is that in no instance was streptomycin therapy directed principally at chronic fibroid, fibrocaseous, or fibrocavernous disease. As in other studies, a number of patients in the present series with such chronic lesions have received streptomycin for acute "spreads" of tuberculosis. The experience of this study is in agreement with other reports that streptomycin in such cases is often of

<sup>1</sup> From the Laurel Heights State Tuberculosis Sanatorium, Shelton, Connecticut.

<sup>2</sup> This study is part of the Streptomycin-Tuberculosis Research Project of the American Trudeau Society, Medical Section, National Tuberculosis Association. The drug was generously donated to the Society by Abbott Laboratories, Eli Lilly and Company, Merck and Company Inc., Charles Pfizer and Company, Inc., E. R. Squibb and Sons, and the Upjohn Company.

<sup>3</sup> This study was aided by grants from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service.



extremely great value as an adjunct to major collapse therapy or to resection, but that it is rarely adequate alone for the treatment of the chronic component.

The present report is concerned not with the action of streptomycin against associated acute disease, nor with its action (or lack of it) against chronic fibroid, fibrocascous, or fibrocavernous disease as such. This report is concerned rather with the action of streptomycin against other types of subacute and chronic tuberculosis.

Another matter which merits mention is the use of terms in the subsequent discussion. The terms subacute and chronic are used here in their literal sense to describe lesions known to have existed for considerable periods of time prior to the institution of streptomycin therapy. These terms are not used with implications as to pathological changes. In roentgenograms, the lesions to be discussed showed, with few exceptions, little or none of the "soft" quality commonly thought to be an indication of predominantly exudative disease. The roentgenographic appearance of the densities was, rather, that which the writers have come to associate with lesions deemed to be predominantly productive in character. It is admittedly difficult to draw such inferences from roentgenograms with accuracy and such attempts introduce to a major degree the element of personal judgment on the part of the observer. Some clinicians who have reviewed the records of these patients with disseminated lesions have felt that the demonstration of marked clearing in serial roentgenograms during and after treatment constitutes evidence, in retrospect, that the lesions were actually exudative. Other clinicians have preferred to designate all lesions which subsequently cleared as subacute, thus avoiding the term chronic for these cases. The writers prefer to leave all pathological inferences to the pathologist and in the subsequent discussion will merely describe the roentgenographic appearance of the lesions and indicate their duration. The reader may, if he wishes, draw his own conclusions from the roentgenograms of illustrative cases reproduced below.

A discussion of whether a given lesion is subacute or chronic is largely in the realm of semantics. To divide the lesions into subacute and chronic categories would be both arbitrary and useless, especially in view of the fact that, in many cases, the various increments contributing to the total disease present were known to differ considerably in age. The term subacute would seem proper when the observed and known duration of the principal disease was approximately six months or less; but when tuberculous disease passes its first birthday and enters its second year it is well along on the road to chronicity. Lesions of various ages are grouped together in the discussions which follow.

## CLINICAL OBSERVATIONS

### *Tracheobronchial disease*

Two types of subacute and chronic tuberculosis will be the subject of passing comment only. The excellent response of ulcerative tuberculous bronchitis and laryngitis to streptomycin therapy has been reported by others (5, 6, 10), and was also observed in this study.

Among the patients with ulcerative tuberculous bronchitis are two who are noteworthy. The ulcerative endobronchial disease had fluctuated in extent and had persisted under repeated observation in one patient for more than five years, in the other for more than two and one-half years, prior to treatment with streptomycin. The lesions were observed to heal within nine and four weeks, respectively, after the institution of streptomycin, and both were still healed when observed nine months later. In another patient, an old and recurrently

active tuberculous laryngitis of ten years' standing had shown steady progression with eventual ulceration during the six months prior to streptomycin therapy. Response to streptomycin was dramatic, with rapid healing of the ulceration, and with gradual return to an essentially normal appearance by the end of four months of treatment. The larynx has remained healed during the year of observation since streptomycin treatment was terminated.

*Cavity Closure:* Among the patients with cavity were six with single or multiple round, thin-walled cavities which were not associated with dense conglomerate or fibrous disease. The cavities had increased in size or remained unchanged during six months or more of observation at bed-rest prior to streptomycin therapy. Under treatment with streptomycin, all cavities appeared to close in four patients. In the other two patients, cavities became markedly reduced in size but never closed. It is believed that these were "blocked" or tension cavities, and, as suggested by Muschenheim and his associates (7), the principal action of the streptomycin in these cases was probably exerted on tuberculous involvement of the draining bronchi. In two of these patients, cavities which appeared closed for a time subsequently reopened; the cavities which had only become smaller subsequently increased in size again. On the basis of the experience with these and other "tension" cavities, it appears that streptomycin alone will only occasionally accomplish permanent cavity closure when bed-rest has failed. Streptomycin may, however, be an extremely valuable aid to the closure of such cavities by collapse therapeutic procedures.

### *Subacute and Chronic Pulmonary Tuberculosis*

The subsequent discussion will be devoted to a more detailed presentation of the results observed in two types of subacute and chronic pulmonary tuberculosis. As mentioned above, the patients in these two categories constitute only a part of the patients included in the entire streptomycin study, the results of which are reported elsewhere (11).

### *"Grumblers"*

The term "grumblers" has been employed to describe in a word a special group of truly chronic cases of pulmonary tuberculosis which have been subjected to streptomycin therapy. The "grumblers" are patients whose disease had always been limited in extent, or whose previously more extensive tuberculosis had improved quite satisfactorily up to a point. Hence, both roentgenologically and clinically the status of all appeared favorable. Nevertheless, all the patients in this category had been unable to stabilize and arrest their disease completely, in spite of long, often multiple, periods of sanatorium treatment, and in spite of trials of phrenic paralysis and pneumothorax when these had seemed to be indicated. Instead, sputum or gastric contents from all these patients had continued to be positive for tubercle bacilli on most examinations, and recurrent episodes of minor instability of disease, as determined by roentgenograms, had been the rule.

Except for the readiness with which tubercle bacilli were found, these patients

appear to correspond clinically to some of the patients with "indolent" tuberculosis described by Gloyne (12). In the majority of the present series, residual pulmonary disease was bilateral in distribution. One patient had a recurring small cavity which was present when treatment with streptomycin was started; in the remainder, no definite cavity could be outlined even with planigrams. Several patients had had tuberculous endobronchial lesions observed at one time or another, and in three patients such lesions were present at the start of streptomycin therapy. In no case, however, could the entire "grumbling" course of disease be explained on the basis merely of chronic cavity or persistent *visible* endobronchial disease. Two typical cases reported below serve to illustrate the type of patient included in this category.

The total period of observation of individual patients prior to streptomycin treatment ranged from one and one-half to twenty years. Some patients, however, had made an apparently good recovery at first, only to relapse later into the "grumbling" course. More pertinent, therefore, is the period during which this persistently "grumbling" course of disease had been observed. In no case had this status existed less than one year, in most patients it had existed more than two years, and in two patients it had existed more than ten years.

It was decided to explore the potentialities of streptomycin in this group of patients for three principal reasons:

(1) They present a serious problem of chronic invalidism which was not being satisfactorily resolved by conventional methods of therapy.

(2) The incidence of the problem is significant in a sanatorium treating chronic tuberculosis.

(3) It was believed that the "grumbling" course of disease, at least in some patients, might well be due to chronic endobronchial tuberculosis beyond the range of bronchoscopic vision. As in other patients streptomycin had already demonstrated a striking effectiveness against active visible endobronchial lesions, even when these were quite chronic, trial of streptomycin for these "grumblers" appeared rational.

*Clinical and roentgenologic course of "Grumblers" under chemotherapy:* Eleven patients in this category have now been treated with streptomycin, and observed for six months or longer since the beginning of streptomycin treatment (four and one-half months or longer since the end of treatment). The period of observation from the beginning of treatment has varied from six to thirteen months. Two of the patients received 2.0 grams of streptomycin daily for one hundred and twenty days, one patient received 2.0 grams daily for sixty-two days, eight patients received 1.0 gram daily for forty-two days only. The status of all these patients, both symptomatically and by roentgenogram, was either fairly good or very good even before treatment. Hence clinical improvement has been slight to moderate only, and in no case has improvement by roentgenogram been more than slight at any time except in the one patient with cavity who obtained cavity closure. Even so, distinct improvement, characterized by an improved sense of well being, gain in weight, and reduced expectoration, has occurred in eight of the eleven patients, and definite "hardening" and retraction of some of the densities seen in roentgenograms has also been observed in eight patients.

Obviously, definitive evaluation of streptomycin in patients with such chronically unstable tuberculosis cannot be made this soon. Tentative evaluation is best based, at this time, on the status of sputum and gastric contents.

TABLE 1  
*Sputum status of "grumblers"*  
(May 1, 1948)

PATIENTS	OBSERVATION PERIOD IN MONTHS SINCE STARTING STREPTOMYCIN	OBSERVATION PERIOD IN MONTHS SINCE STOPPING STREPTOMYCIN	SUMMARY OF FINDINGS IN SPUTUM AND GASTRIC CONTENTS SINCE START OF STREPTOMYCIN, (INCLUDING NUMBER OF POSITIVE AND NEGATIVE REPORTS BY VARIOUS METHODS OF EXAMINATION)*	PRESENT STATUS OF SPUTUM AND GASTRIC CONTENTS**
H. P.	13	11	Consistently + 2 months; then neg. (15 S, 6 C, 2 G. P.), but with isolated + reports (1 S, 3 C, 1 G. P.)	Neg. 4 months
M. H.	13	9	Consistently + 1 month; then consistently neg. 8 months (19 S, 14 C, 8 G. P.), then relapse and again +	Consistently +
A. S.	13	9	Consistently + 1 month; then consistently neg. 12 months (21 S, 15 C, 8 G. P.)	Neg. 12 month
M. B.	8½	7	Consistently + 1 month; then neg. 7 months (7 S, 2 C, 1 G. P.) except for 1 isolated + spec. (S & C)	Neg. 4 months
E. G.	8½	7	Consistently + 1 month; then neg. 7 months (5 S, 4 C, 2 G. P.) except for 1 isolated + spec. (S & G. P.)	Neg. 3 months
M. G.	8½	7	Consistently + throughout	Consistently +
C. P.	8½	7	Consistently + 1½ months; then consistently neg. 3 months (4 S, 2 C, 2 G. P.); then relapse and again +	Consistently +
T. V.	8½	7	Consistently + 4 months; then neg. except for 1 spec. (+ S, neg. C)	Neg. 2 months
C. C.	6	4½	+ by 1 C only since start of treatment; otherwise neg. (7 S, 2 C)	Neg. 3 months
A. P.	6	4½	Consistently neg. since start of treatment, (7 S, 5 C, 1 G. P.)	Neg. 6 months
S. S.	6	4½	+ 1 month; then consistently neg. (7 S, 4 C, 1 G. P.)	Neg. 5 months

\* Key: S = Smear of concentrated sediment.

C = Culture

G. P. = Guinea pig inoculation

+ = positive, neg. = negative.

\*\* C and G. P. of specimens obtained within last month not yet reported.

*Bacteriologic course of "Grumblers" under chemotherapy:* In all eleven patients, the sputum or gastric contents were positive by smear for tubercle bacilli (confirmed by culture) prior to streptomycin treatment. Table 1 records the findings during and after treatment. It has been the usual practice to obtain specimens of gastric contents for examination periodically as soon as sputum became

either unavailable or negative once or twice by smear. Nevertheless, examinations of the sputum were continued as well so long as expectoration continued. After treatment was started, most specimens of sputum and all specimens of gastric contents were cultured. In addition, a number of specimens were also inoculated into guinea pigs. A specimen of sputum has been called positive if acid-fast bacilli were found by either smear, culture, or guinea pig inoculation. A specimen of gastric contents has been called positive if either culture or guinea pig was positive. Occasionally acid-fast bacilli were found in gastric contents by smear, but tubercle bacilli could not be demonstrated by either culture or guinea pig inoculation of the same specimen; such smears have been excluded from the data in table 1.

It may be seen in table 1 that really complete and sustained sputum conversion has been achieved, thus far, in only a few patients. In one patient, the sputum has remained consistently positive throughout the entire observation period. Two patients, after eight and three months, respectively, of consistently negative sputum and gastric contents, subsequently relapsed. A cavity reopened in one and a small spread of infiltration appeared in the other. The sputum of both patients again became positive for tubercle bacilli. The remaining eight patients have had varying periods of negative sputum and gastric contents, and have maintained or further improved their favorable clinical and roentgenographic status during the observation period since treatment was stopped. In several however, the observation period with sputum negative is relatively short, with the most recent cultures not yet reported; in several others, longer periods during which negative reports were the rule have been marred by the recurrence of at least isolated positive reports.

It should be realized, however, that in the streptomycin treated patients the search for tubercle bacilli has generally been far more frequent, and that examinations by culture and guinea pig inoculation have been made much more often since streptomycin was administered than before. In contrast to the data recorded in table 1, tubercle bacilli were readily and regularly found, prior to treatment, by routine monthly smear of concentrated sputum in nine of these "grumblers"; only two required examination of gastric contents, and none required culture except for confirmation and for sensitivity tests. There is little doubt that streptomycin has produced, at least temporarily, a distinct improvement in the clinical course and in the sputum status of most of these patients. What remains to be determined is whether or not relapse, which has already occurred in two patients, will eventually prove to be the rule.

The results observed thus far are certainly not adequate to justify the routine use of streptomycin therapeutically in cases of this type. The chronically active course of disease in the group as a whole has, however, been sufficiently influenced to suggest the desirability of studying more patients of this type on a purely exploratory basis. Especially in patients with such chronic disease as this, much longer follow-up will be necessary before the definitive value of streptomycin can be determined.

The following two cases illustrate several of the points made in the preceding paragraphs:

#### CASE REPORTS

*Case 1*, A. S., was a 38-year-old white female. The roentgenogram (figure 1) shows the limited amount of bilateral pulmonary tuberculosis visible just prior to streptomycin treatment in a typical "grumbler". First seen in 1927, this patient had originally had much more extensive disease which had been treated between 1927 and 1931 with pneumothorax on both sides, with apparently good results. For the ten year period between 1936 and March 31, 1947 (when streptomycin was started), the appearance of the disease in

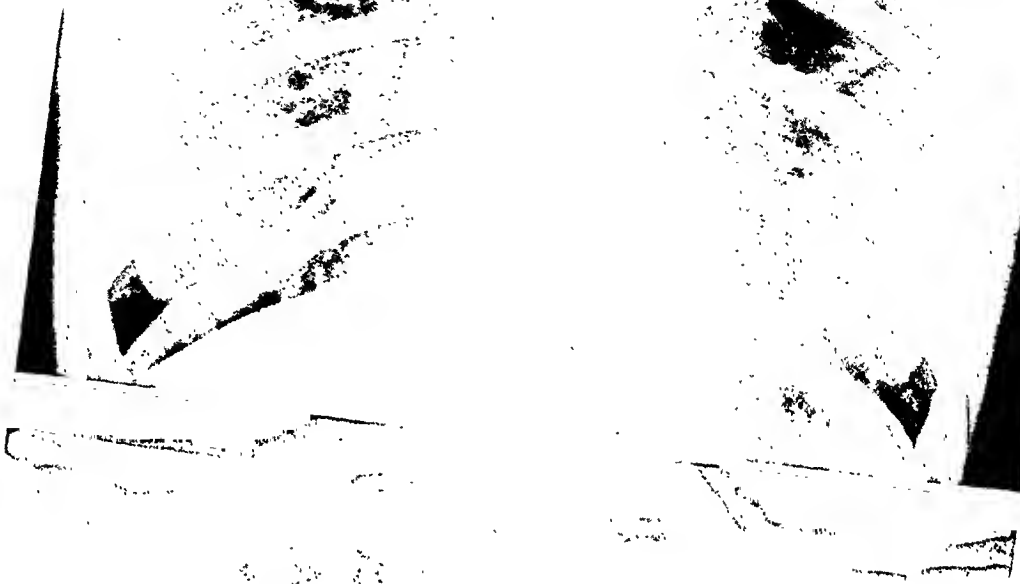


FIG. 1. Case 1. March 13, 1947. Shortly before start of streptomycin treatment.

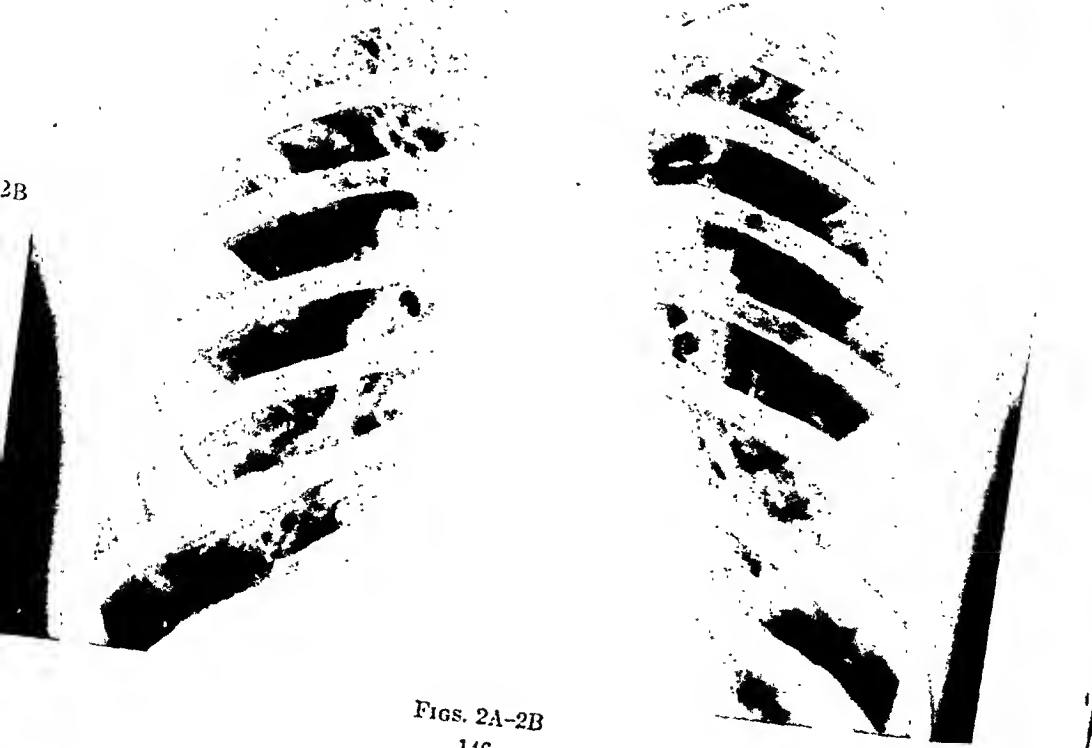
roentgenograms had, except for recurrent minor instability, been much the same as that shown in this film. Nevertheless, sputum had been consistently positive for tubercle bacilli all this time and exacerbations of symptoms, including hemoptysis, had occurred several times. The patient had been readmitted to the sanatorium four times and had spent a total of six years within the sanatorium since 1936. Both bed-rest and right phrenic paralysis had failed significantly to influence the chronically unstable course of disease. A visible endobronchial lesion, present in 1940, had been reported healed after the end of that year and was not present when treatment with streptomycin was started. No definite cavity was visible.

Following treatment with streptomycin for one hundred and twenty days (2.0 grams daily) the improvement observed by roentgenogram in this case was minimal, but symp-

2A



2B



Figs. 2A-2B  
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toms improved and sputum has now been consistently negative by smear, culture, and guinea pig inoculation for more than eleven months (see A.S., table 1).

*Case 2, H. P.*, was a 31-year-old white female (figure 2). This patient was first seen in January, 1942, with moderate involvement of both upper lobes but without cavity.

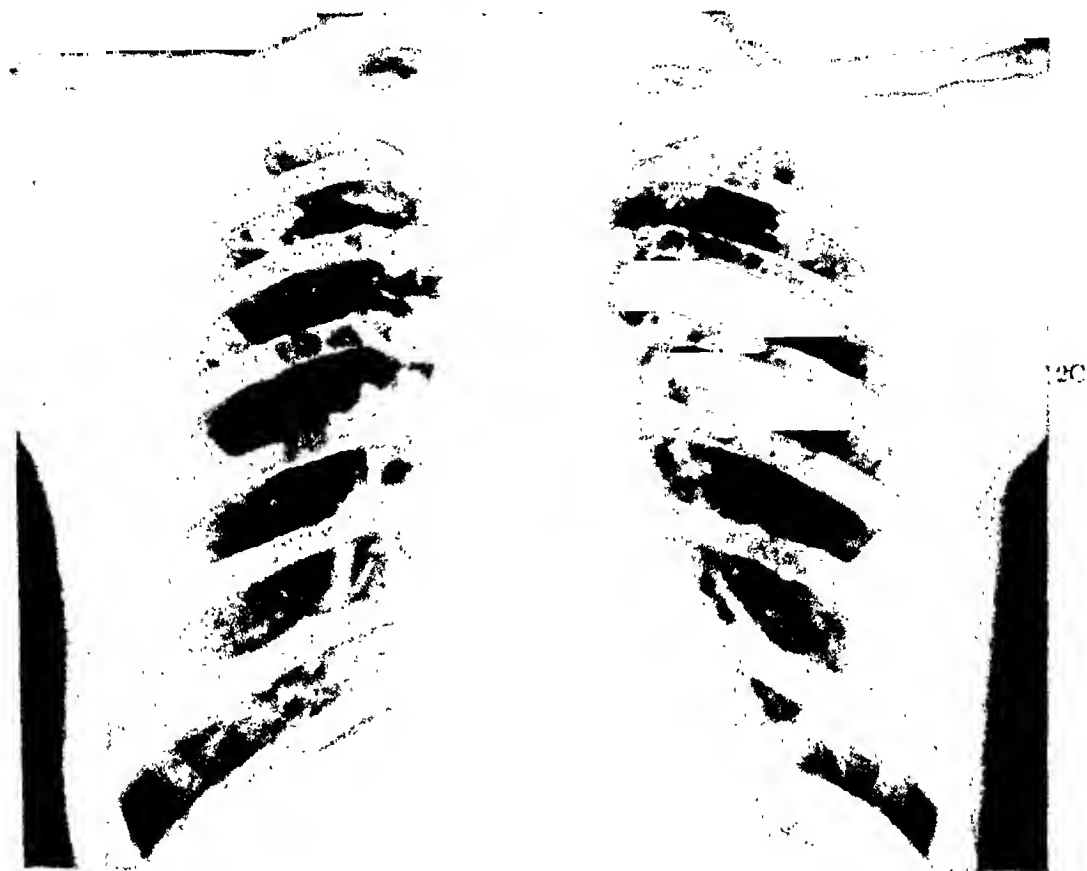


FIG. 2A. Case 2, February 12, 1945. Twenty-five months preceding streptomycin treatment.

FIG. 2B. Case 2, March 19, 1947. Shortly before start of streptomycin treatment.

FIG. 2C. Case 2, December 13, 1947. Eight months after start of treatment after end of streptomycin treatment.

Sputum contained tubercle bacilli. On bed rest there was roentgenographic improvement and conversion of sputum, and the patient was discharged in May, 1943. Because of the recurrence of positive sputum, she was readmitted in November, 1943. Roentgenograms showed questionable instability in the right lung but no gross improvement of disease (figure 2A). In spite of bed rest, ineffective right pneumothorax, properly administered, and the institution of tuberculin desensitization plus pyridoxine, sputum continued to be positive for tubercle bacilli. Cavity could not be demonstrated in either the ventral or dorsal projections. A roentgenogram taken on the right upper lobe, by means of a lead shield against the rest of the chest, in March, 1947, revealed no cavity but a nodular shadow. During the next three to four years of intermittent treatment, which preceded the present



streptomycin, there had occurred insidious slight increases of the disease in both upper lobes (figure 2B). Because of the "grumbling" nature of the disease, streptomycin therapy was begun on March 31, 1947, and was continued for sixty-two days (2.0 grams daily). Streptomycin was then discontinued because of troublesome chronic skin rash, which subsided completely after chemotherapy was stopped. Roentgenograms at the end of treatment showed slight clearing, and further slight clearing has occurred during a ten month posttreatment period (figure 2C). The patient's clinical status is definitely improved. Sputum became negative after completion of treatment and is negative by recent smear and culture. True sputum conversion is, however, uncertain in this case (H. P., table 1). A specimen of gastric contents obtained in December, 1947, was positive for tubercle bacilli by culture. In cases such as this, more time will be required to determine whether the eventual outcome will be true arrest of disease, or relapse and reversion to a chronically active and unstable status.

### Disseminated Nodular Pulmonary Tuberculosis

Several investigators have noticed that good response of pulmonary tuberculosis to streptomycin is more likely to occur if the individual densities seen in roentgenograms are relatively small and disseminated in character than if the lesions are grossly confluent and massive. The excellent response of disseminated lesions was noted, in fact, among the very early cases treated by Hinshaw. (3, 4). In the cases which had been reported prior to the inauguration of the present study, however, the disseminated lesions were either known or presumed to be of relatively recent origin, for emphasis upon choosing acute lesions for treatment was strong at that time. In the present study, it was decided to include, also, patients with disseminated lesions of longer duration, provided that these had failed to respond to bed-rest in the pretreatment period. This decision was influenced by the fact that the investigators had previously seen other patients with chronic disseminated infiltrations who had responded favorably to long term bed-rest and had shown, by roentgenogram, remarkable clearing of such lesions. Hence, it was believed that these lesions were potentially reversible, even when chronic.

The patients included in this category had disseminated nodular infiltrations which differed considerably in total extent. There was some variation, also, in the size of individual nodules and in their degree of confluence. In the typical case the individual nodular densities were relatively small, and were finely distributed throughout the involved lung segments, with confluence of lesions at a minimum. In addition, many of the patients had localized collateral disease of other types (for example, chronic focal infiltrations or cavity), but it was against the disseminated nodular lesions that streptomycin was principally directed (cases 4 and 5).

At the present time, fifteen patients in this category have been treated with streptomycin and observed for a period of four and one-half months or longer from the beginning of streptomycin treatment (three months or longer from the end of treatment). In none of these patients was the disease improving at bed-rest prior to treatment with streptomycin. In only two patients had the disseminated nodular lesions been actually observed for less than six months,

and in each of these patients both the history and the appearance of disease in the first roentgenogram indicated that the lesions were not acute. In these two patients, the disseminated lesions had remained unchanged prior to treatment; in the remaining thirteen patients, the lesions were slowly increasing during observation periods at bed-rest of more than six months. The disseminated nodular disease had been steadily or intermittently progressive for from one to three and one-half years in seven patients. One patient received 1.8 grams of streptomycin daily for 150 days, six received 1.8 or 2.0 grams daily for 120 days, eight

TABLE 2

*Effects of streptomycin on sputa and clinical disseminated nodular tuberculosis*

(May 1, 1948)

RESULTS OF TREATMENT AS TO TREATMENT PERIODS AND TREATMENT DAILY DOSAGE		PATIENTS DISMISSED AS BEING IN REMISSION OF TUBERCULOSIS IN ROENTGENOGRAMS OF PULMONES AND IN STATUS OF SPUTUM AND GASTRIC CONTENTS			
		0 to 42 to 100 mg. daily 1 patient	0 to 60 to 100 mg. daily 3 patients	0 to 4 to 100 mg. daily 1 patient	Total, 5 patients
Clearing observed in serial roentgenograms	Slight			1	1
	Moderate	2	1	1	4
	Marked	3	2		5
	Striking	2	2	1	5
Clinical improvement	Slight	2		2	4
	Moderate	1	3	1	5
	Marked	2	2		4
	Striking	2			2
Overall improvement	Slight			2	2
	Moderate	2	3		5
	Marked	2	1	1	4
	Striking	3	1		4
Status of sputum and gastric contents	Consistently neg. 6 to 11 months	1	1		2
	Negative 1 to 5 months	2	2	2	6
	Still positive	1	2	1	4

received 1.0 gram daily for 42 days. The patients receiving the larger doses were treated first; subsequently the 1.0 gram daily dose was employed.

*Course of disseminated nodular tuberculosis under chemotherapy:* All fifteen patients have shown distinct improvement, both clinically and roentgenographically, during the observation period since streptomycin was started. The degree of improvement has, however, varied considerably in different patients. The results of treatment are summarized in table 2. Clinical improvement was necessarily limited in many of these patients because most of them were in fair to good clinical condition even before treatment with streptomycin. In assessing overall improvement, major weight was given to the change observed on the roentgeno-

grams, but consideration was also given to a patient's age, race and sex, his previous course, and the alteration in prognosis achieved as a result of streptomycin treatment. In tabulating sputum status, the same standards and criteria obtain as were mentioned in the previous section on "grumblers". Of the four patients with sputum still positive, three have definite residual cavities as the source, the other has questionable cavity.

*Roentgenographic clearing:* While the foregoing data are of interest, the clearing of the disseminated nodular infiltrations observed in serial roentgenograms (and recorded in table 2) constitutes the most important and accurate criterion for judging the effect of streptomycin in patients of this group.

In determining how to score the clearing observed in a given patient, it was decided to take into account both the extent of the disease present before treatment and the degree of clearing observed after treatment was instituted. The clearing recorded represents that which occurred during the entire period of observation since treatment was started. A tabulation of clearing observed at the end of treatment is deliberately omitted because the clearing observed at forty-two days provided a very poor index to the total clearing which eventually occurred. A striking example of this is Case 6, who showed virtually no improvement at the end of her forty-two days of treatment, but whose disseminated lesions then cleared steadily until they had almost completely disappeared in roentgenograms made at the end of nine months. As would be anticipated, the patients treated for one hundred and twenty days or longer generally showed a greater amount of clearing at the end of treatment, but even these patients have, without exception, continued to show further clearing of the disseminated densities since treatment was terminated. So far as can be judged from such a small series of patients, there appears to be no consistent difference in the total amount of clearing eventually observed in the patients treated with 1.8 to 2.0 grams of streptomycin daily for one hundred and twenty (or one hundred and fifty) days and in those treated with 1.0 gram daily for forty-two days only. Likewise, rapidity of clearing appeared to be comparable on the two streptomycin regimens.

The rate at which roentgenographic clearing of these lesions has occurred has differed considerably in individual patients. In all of these patients clearing has been distinctly slower than that commonly seen in fresh exudative lesions treated with streptomycin. Beginning improvement and reversal of a previously progressive trend has, however, usually been quite prompt. In general, the older lesions have cleared somewhat more slowly and somewhat less completely than the younger lesions, but the difference has not always been as great as had been expected (see Cases 5 and 6). A most surprising feature has been the rapidity and completeness of clearing of many densities known to have been present for more than a year.

Especially among the older lesions, clearing has been distinctly more rapid and more complete when the individual nodular densities were quite small and discrete than when they were, relatively, larger and more confluent. Even very old chronic lesions may sometimes be affected, however. One patient who was treated principally for widely disseminated fine nodular disease, which had slowly

increased during the previous year, had also very chronic tuberculosis in both upper lobes. This consisted of old linear and irregular nodular densities of various sizes, some of which had been present and recurrently unstable for years. Streptomycin treatment resulted not only in virtually complete disappearance of the newer finely disseminated lesions, but also in partial (though incomplete) clearing and in "hardening" of the old nodular densities which had been present for more than ten years.

In referring to the clearing or to the disappearance of these lesions, the descriptions are made in roentgenographic, not in pathological, terms. In many instances, the clearing has been sufficiently rapid and complete to suggest that actual resolution may well have played a part. Certainly retraction with progressive decrease in size of the individual nodules has also been prominent. For many of the nodular densities, small persistent and presumably permanent residuals are still quite apparent; for others, these residuals cannot be seen, probably because they are simply too small to cast a detectable shadow in roentgenograms.

During the period of observation thus far, no instance of relapse of the disseminated nodular disease has occurred. In one patient an associated cavity, which decreased in size during treatment, has subsequently increased in size, but the associated widely disseminated nodular disease has continued to improve (Case 5). Except for this incident, all patients have continued to show progressive improvement, both clinically and roentgenographically, after treatment with streptomycin was completed.

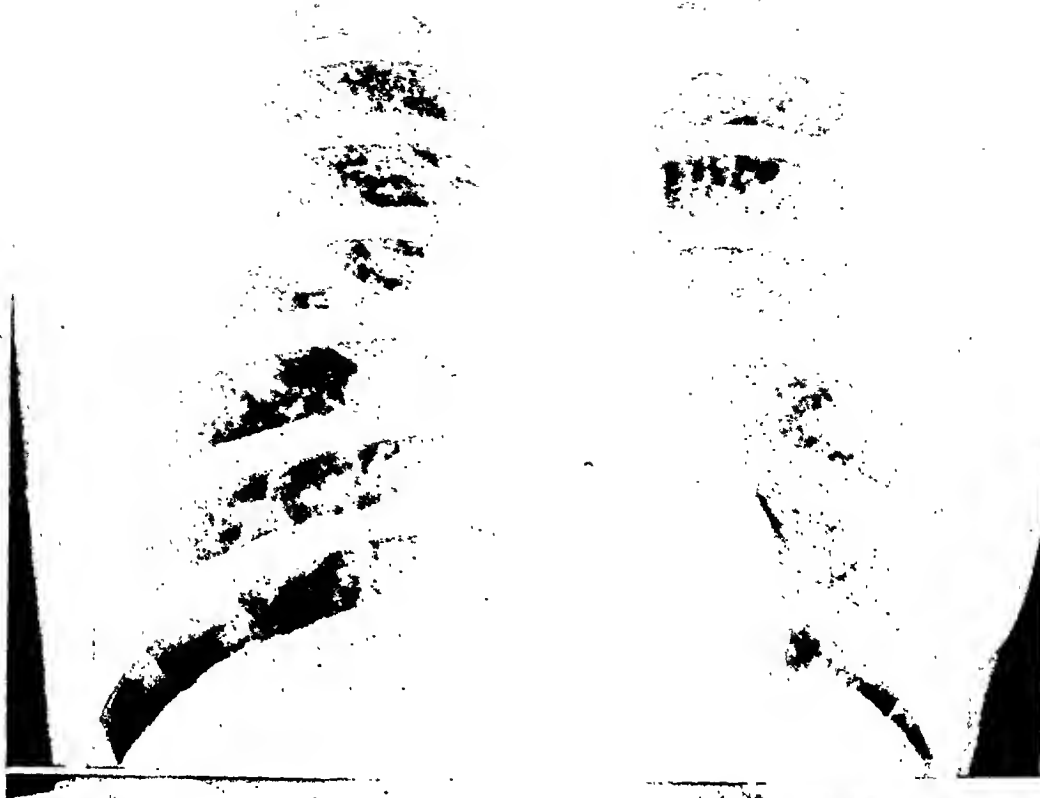
The following case reports constitute representative examples of the type of result observed.

#### CASE REPORTS

*Case 3*, L. R. (figure 3), was a 22-year-old white female who first entered the Cedarcrest sanatorium in April, 1946. Sputum contained tubercle bacilli; there was cough, expectoration, and low grade fever. Roentgenograms showed disseminated nodular and small conglomerate infiltrations throughout both lung fields (figure 3A). On a regimen of strict bed-rest for six months there was some clinical improvement, but serial films showed instability with overall progression of disease bilaterally. Upon transfer to Laurel Heights on November 1, 1946, for treatment of the progressive disseminated disease, the patient became extremely ill. A film on admission confirmed the continued further progression of the disseminated pulmonary disease and demonstrated, also, the development of an acute pleural effusion on the right (figure 3B). Bronchoscopy revealed no evidence of tuberculous bronchitis. The pleural effusion was confirmed by thoracentesis of 250 cc. of clear fluid which was negative upon culture for tubercle bacilli, but which was typical in appearance of tuberculous effusion. Being extremely dyspneic, the patient was placed on oxygen therapy, and streptomycin therapy (1.8 gram daily) was started on November 6, 1946.

Symptomatic improvement promptly followed; with rapid complete clearing of the pleurisy within a week, with only low grade fever after the tenth day, and with temperature entirely normal after the sixtieth day of treatment. Further clinical and roentgenographic improvement was gradual but steady during the one hundred fifty days of treatment. At the end of treatment, sputum was negative for tubercle bacilli and there was very striking clearing of the extensive disseminated fine nodular and conglomerate disease

3A



3B

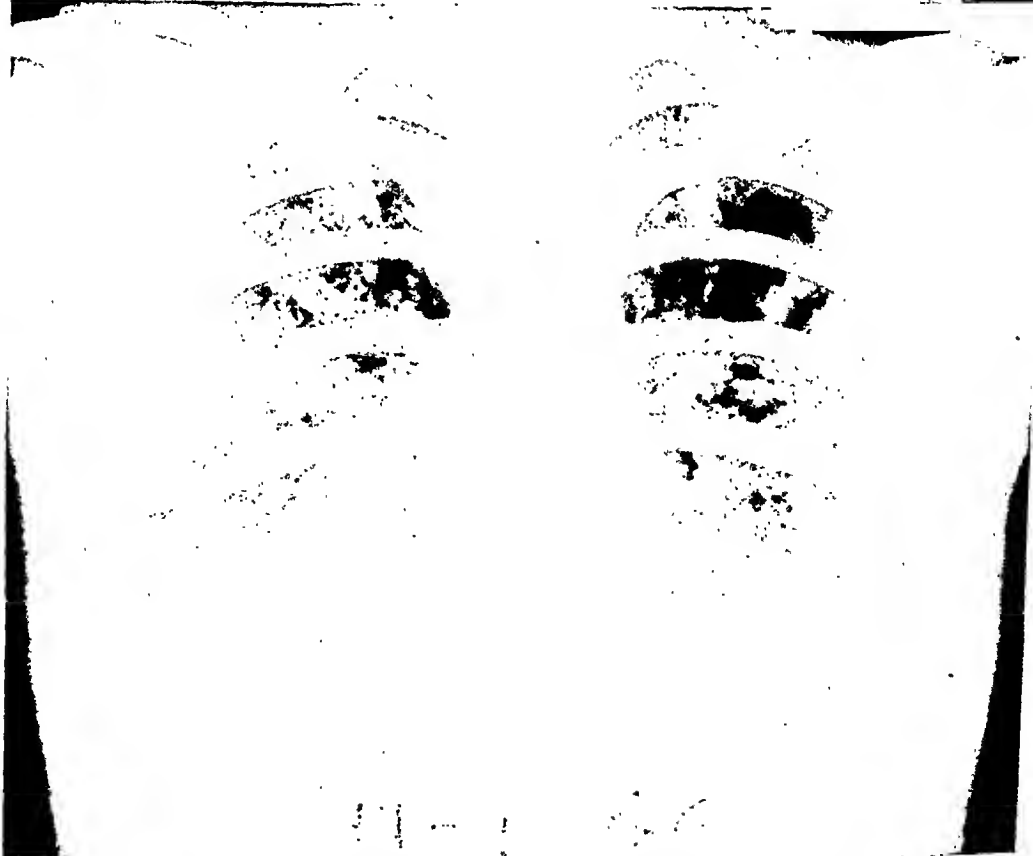
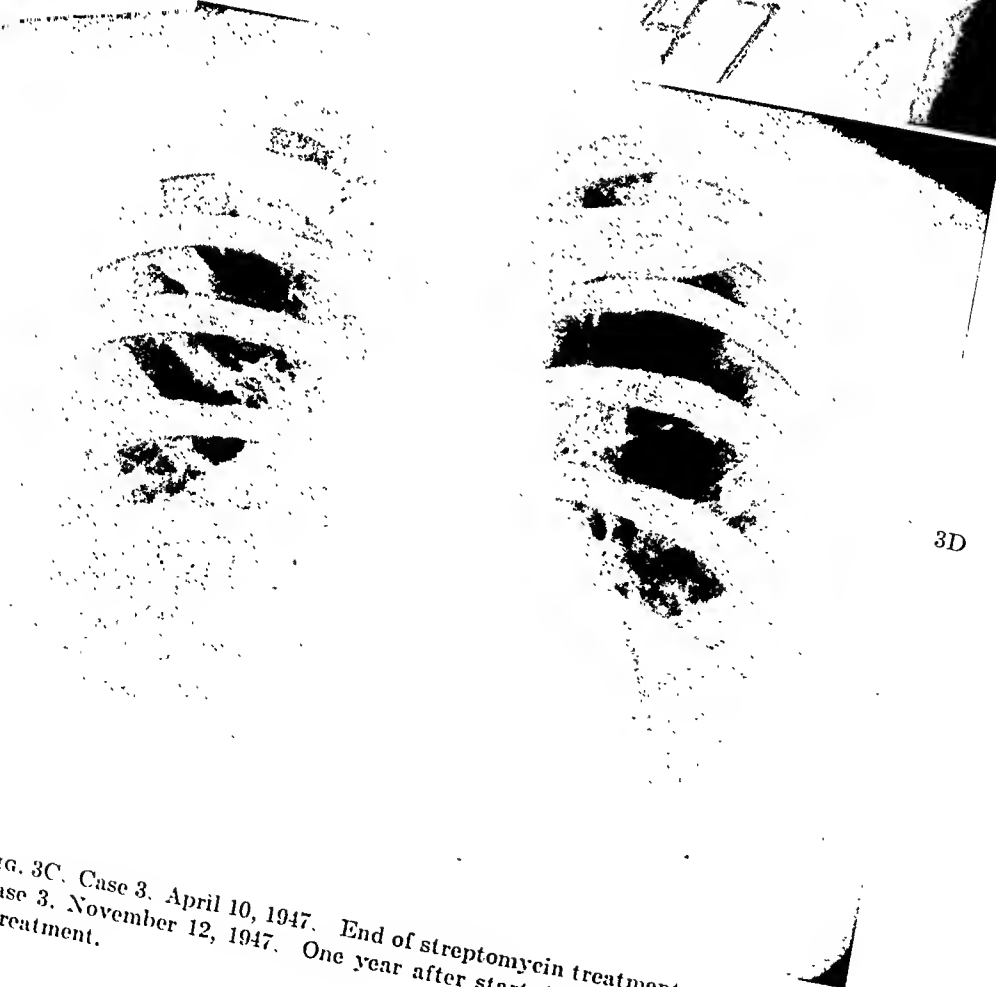


FIG. 3A. Case 3. April 25, 1946. Six months preceding streptomycin treatment.  
FIG. 3B. Case 3. November 1, 1946. Just before start of streptomycin treatment.



3C



3D

FIG. 3C. Case 3. April 10, 1947. End of streptomycin treatment.  
 FIG. 3D. Case 3. November 12, 1947. One year after start (7 months after end) of streptomycin treatment.

(figure 3C). On continued sanatorium treatment, sputum and gastric contents have remained negative except for isolated positive sputum cultures in July and November, 1947. During the seven months after completion of streptomycin treatment, there was some further clearing in serial roentgenograms (figure 3D), and this improved status has been well maintained to the present time (May 1, 1948). The patient is now beginning outside walking exercise.

The subacute disseminated disease present in this case prior to treatment was more active clinically and the size of individual densities was more irregular and less uniform than in most of the patients in this disease category.

*Case 4, A. R.* (figure 4), was a 21-year-old white female. Onset of definite pulmonary symptoms occurred in this patient around February, 1946, but a diagnosis of pulmonary tuberculosis was not made until approximately six months later. On admission to the Undercliff Sanatorium in August, 1946, roentgenograms showed disseminated small nodular infiltration throughout both lungs, with three thin walled cavities present; two on the right, one on the left. The patient failed to improve at bed-rest and was transferred to Laurel Heights for inclusion in the streptomycin study. A new film, made on November 11, 1946, the day streptomycin was started, showed no change when compared to the August film except for the enlargement of one of the cavities on the right (figures 4A and 4C). No endobronchial disease was seen by bronchoscopy. Treatment with streptomycin was continued for one hundred twenty days (1.8 gram daily).

Upon completion of treatment there was marked clinical improvement, the sputum was consistently negative for tubercle bacilli, and a roentgenogram showed marked clearing of the disseminated nodular disease (figures 4B and 4D). Also there was complete closure of all cavities. Since then there has been further clearing on serial films and sputum and gastric contents have now been consistently negative for ten months.

This is one of the most striking instances of sustained cavity closure (without collapse therapy) observed in the entire series of streptomycin treated cases. The clearing of the nodular infiltrations is, however, typical of that observed in other patients with subacute and chronic disseminated lesions of this type.

Figures 4C and 4D were reproduced to larger scale better to show the nodular lesions before and after treatment. In all cases these small densities are, however, hard to reproduce in print; the clearing is more apparent and more striking in the actual roentgenograms.

*Case 5, E. M.* (figure 5), was a 26-year-old white female. During the early weeks of treatment by bed-rest, this patient had improved clinically, and serial films had shown satisfactory (though incomplete) clearing of soft irregular mottled tuberculous infiltration present in the right upper and lower lobes. After this clearing had taken place, the appearance of disease on the roentgenogram was that shown in figure 5A. The left lung was then clear except for a few residual densities at the apex and base. Sputum was positive for tubercle bacilli.

Beginning in 1943 there was, however, gradual progressive seeding of both lungs with finely disseminated small nodular densities, which increased steadily in number and in extent throughout three and one-half years of observation between March, 1943, and November, 1946. While the patient continued to be afebrile and while there was further clearing for a time in the localized "soft" infiltration, the slowly progressive course of the



11



12

13. 14. 15. 16. 17. 18. 19. 20. 21. 22. 23. 24. 25. 26. 27. 28. 29. 30. 31. 32. 33. 34. 35. 36. 37. 38. 39. 40. 41. 42. 43. 44. 45. 46. 47. 48. 49. 50. 51. 52. 53. 54. 55. 56. 57. 58. 59. 60. 61. 62. 63. 64. 65. 66. 67. 68. 69. 70. 71. 72. 73. 74. 75. 76. 77. 78. 79. 80. 81. 82. 83. 84. 85. 86. 87. 88. 89. 90. 91. 92. 93. 94. 95. 96. 97. 98. 99. 100.



4C

4D

FIGS. 4C and 4D. Case 4. Lower half of left lung reproduced from roentgenograms shown in 4A and 4B, respectively. The clearing of the nodular lesions is better seen in these larger scale reproductions.

disseminated disease was unchecked by bed-rest, by the performance, twice, of temporary right phrenic paralysis, and by a brief trial of supplementary pneumoperitoneum. Right pneumothorax was not attempted because of previous pleurisy on that side. Sputum continued to be consistently positive for tubercle bacilli. The roentgenogram reproduced in figure 5B shows an intermediate stage in the development of the widely disseminated small nodular lesions. By November 11, 1946, when treatment with streptomycin was



FIG. 5A. Case 5. March 11, 1943. Three and one-half years preceding streptomycin therapy.

started, both lungs were extensively involved more or less throughout (figures 5C and 5F). Planigrams prior to treatment showed, also, the presence of cavity in the right lower lobe and another cavity, previously unsuspected, in the right apex. Bronchoscopy showed ulcerative tuberculous bronchitis involving the orifice of the right upper lobe bronchus and several divisions of the right lower lobe bronchus.

Treatment of this patient with streptomycin for one hundred twenty days (1.8 gram daily) resulted in distinct, though incomplete, clearing of the previously progressive disseminated nodular disease (figure 5D). The cavity in the right lower lobe was still present, though smaller; the cavity in the right apex could no longer be definitely visual-

ized; the ulcerative tuberculous bronchitis had healed; the patient's clinical status had improved.

During the thirteen months since streptomycin treatment was completed, the cavity in the right lower lobe has again increased considerably in size, but serial films have shown continued further improvement in the disseminated nodular disease (figures 5E and 5G)



FIG. 5B. Case 5. June 11, 1945. Seventeen months preceding streptomycin therapy.

Sputum continues to be consistently positive for tubercle bacilli. A right lower lobectomy has been recommended.

Figures 5F and 5G were made from the roentgenograms reproduced in figures 5C and 5E, respectively. These larger scale reproductions serve better to show the small disseminated lesions, which are so hard to reproduce clearly in print.

*Case 6, E. B.* (figure 6), was a 30-year-old white female who was admitted in October, 1945, with minimal linear and nodular infiltration in both upper lobes and with residual pleurisy with effusion at the left base. Tubercle bacilli were present in gastric contents.

After eight months of bed-rest, there was clinical improvement but little change roentgenographically except for clearing of the left basal pleurisy (figure 6A).

Upon further continued bed-rest of thirteen months' duration, the small nodular infiltrations increased gradually and insidiously in both lungs, more so on the left (figure 6B). There was low grade fever and fatigue. Gastric lavage continued to show tubercle bacilli. Bronchoscopy in May, 1946, and July, 1947, revealed no endobronchial lesion.



FIG. 5C. Case 5. November 1, 1946. Start of streptomycin therapy.

Because of the progressive fine nodular disseminated type of disease, streptomycin treatment was started on July 6, 1947. After forty-two days of treatment (1.0 gram daily), chest films revealed only slight change (figure 6C). However, gastric washings no longer contained tubercle bacilli. On continued bed-rest in the sanatorium during an eight month posttreatment period, there has been marked further clearing of the previously progressive disseminated nodular disease (figure 6D). Gastric washings have continued to be consistently negative for tubercle bacilli.

This patient provides an excellent example of the "delayed resolution" usually seen in this type of disease.

#### Collateral Observations

*Ulcerative tuberculous bronchitis:* (table 3). Unless specific contraindications existed, all patients were bronchoscoped prior to treatment.<sup>4</sup> If a lesion of the

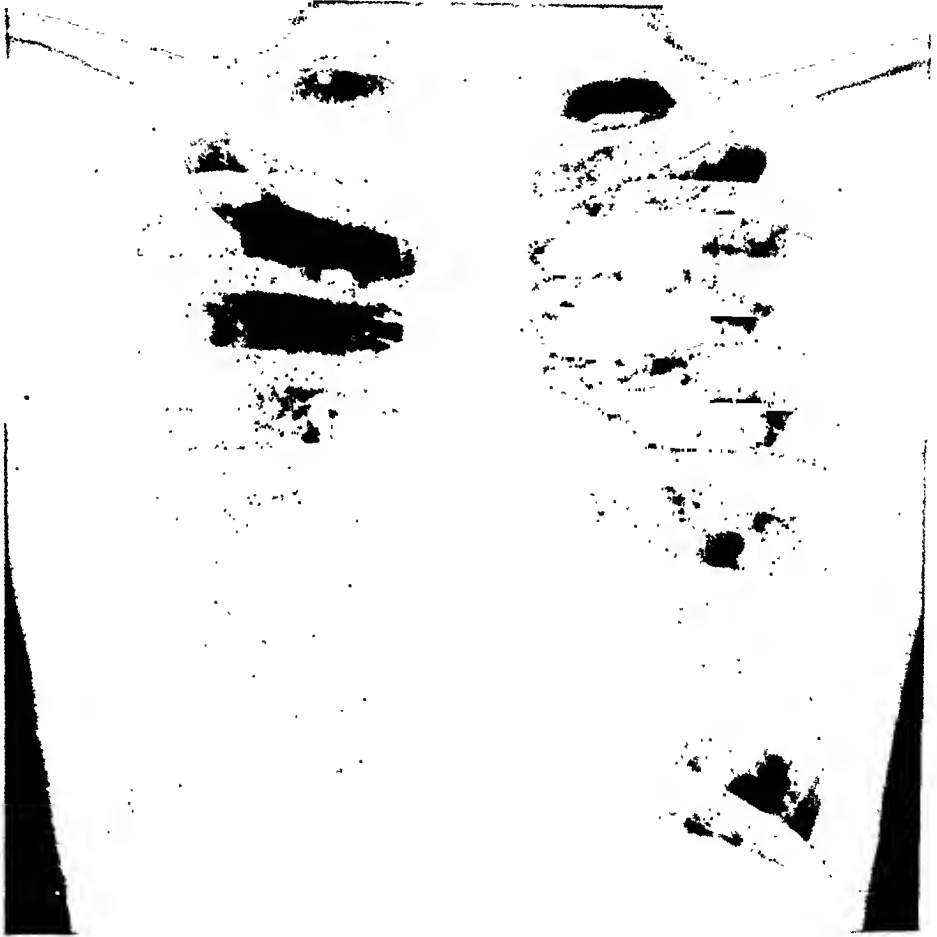


FIG. 5D. Case 5. March 18, 1947. Soon after end of streptomycin therapy.

bronchial mucosa was seen, bronchoscopy was repeated at intervals of four to six weeks until the lesion was deemed healed. Thereafter bronchoscopy was performed only if indicated by symptoms or if relapse was suspected.

Among the patients with the disseminated type of disease there were seven with visible endobronchial ulcerations prior to streptomycin treatment. Upon completion of treatment, the ulcerative lesion was deemed healed in six patients.

<sup>4</sup> All bronchoscopies were done by Dr. W. O. Kelley, Chief Thoracic Surgeon, Connecticut State Tuberculosis Sanatoria.

and improved in one patient. The latter lesion subsequently went on to complete healing.

In the patients whose disease was of a chronic "grumbling" character, there were three patients with visible endobronchial ulcerations. All were deemed healed at the end of treatment.

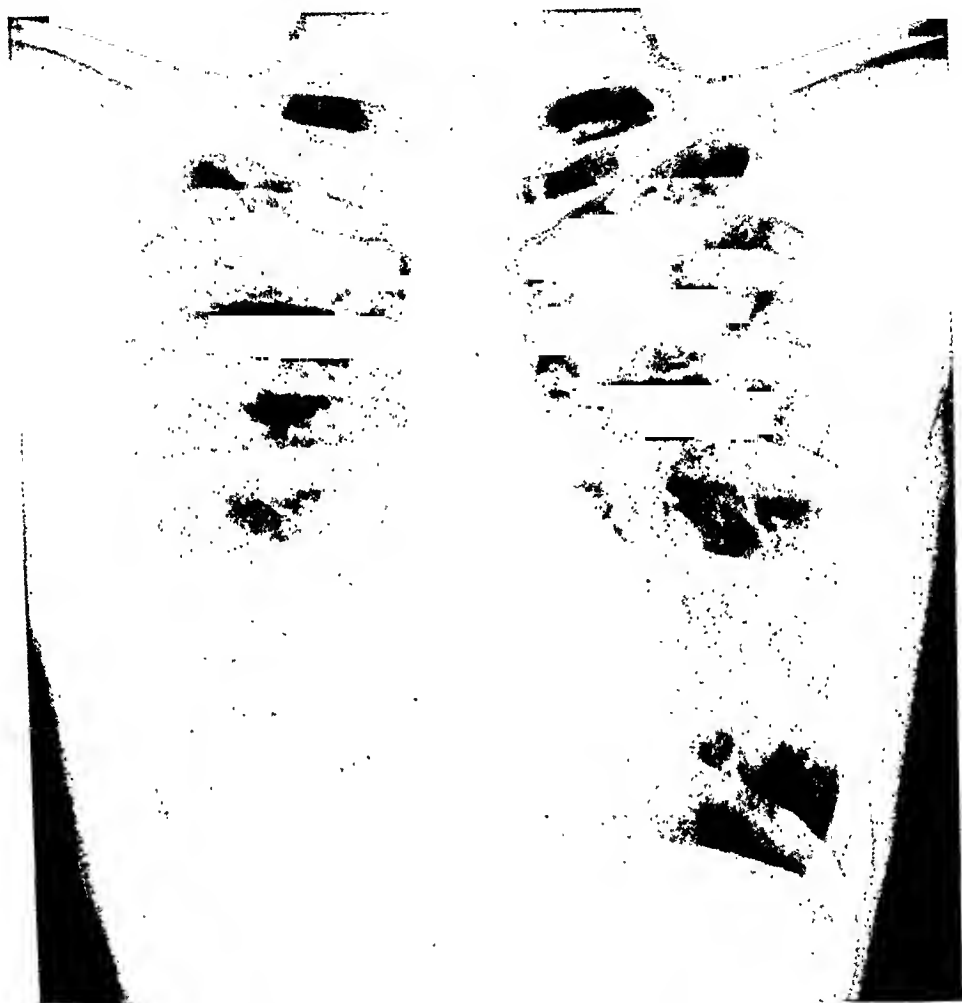


FIG. 5E. Case 5. December 3, 1947. Thirteen months after start (9 months after end) of streptomycin therapy.

Thus far, relapse of endobronchial disease has been observed in only one patient in either of these two disease categories. Ulceration reappeared in a "grumbler" along with relapse of pulmonary disease and recurrence of positive sputum approximately four months after completion of treatment.

*Toxic Manifestations:* (table 4). The toxicity of streptomycin differs in different patients, but is influenced, so far as is known, not by the type of disease being treated but by the treatment regimen being employed. The common toxic



FIG. 5F  
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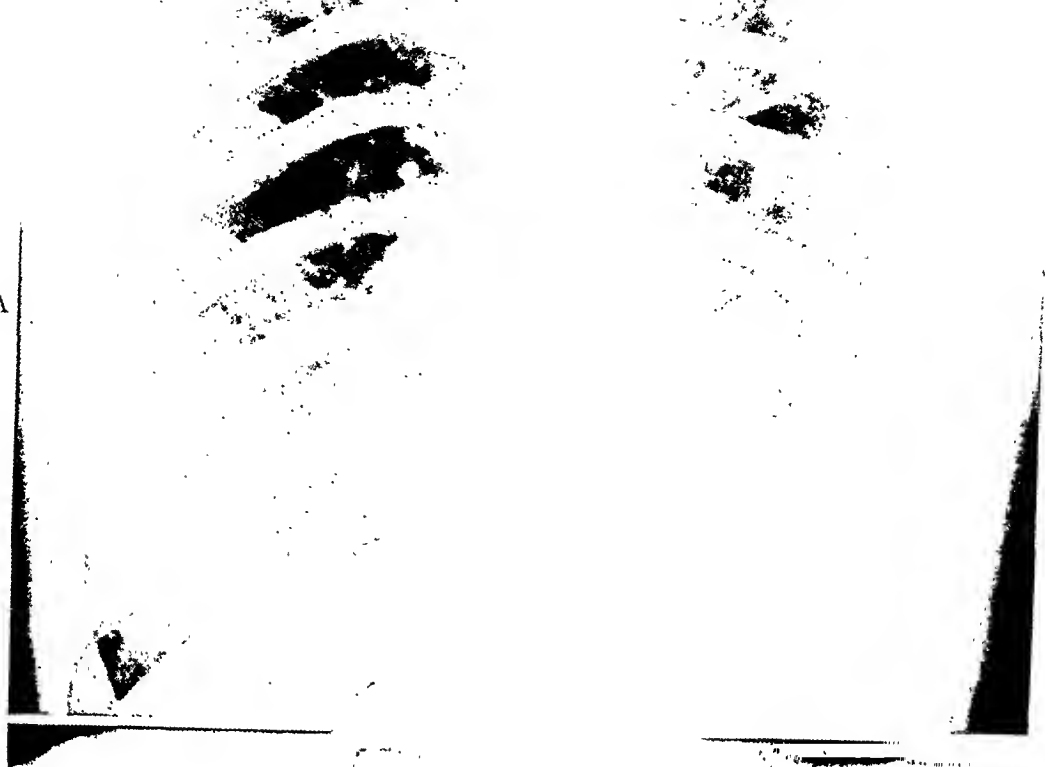


FIG. 5G

FIG. 5F and 5G. Case 5. Lower two-thirds of left lung reproduced from roentgenograms shown in 5C and 5E, respectively. Both the appearance of disease and the clearing between films is better seen.



6A



6B



FIG. 6A. Case 6. June 7, 1946. Thirteen months preceding streptomycin therapy.  
FIG. 6B. Case 6. July 2, 1947. Start of streptomycin therapy.

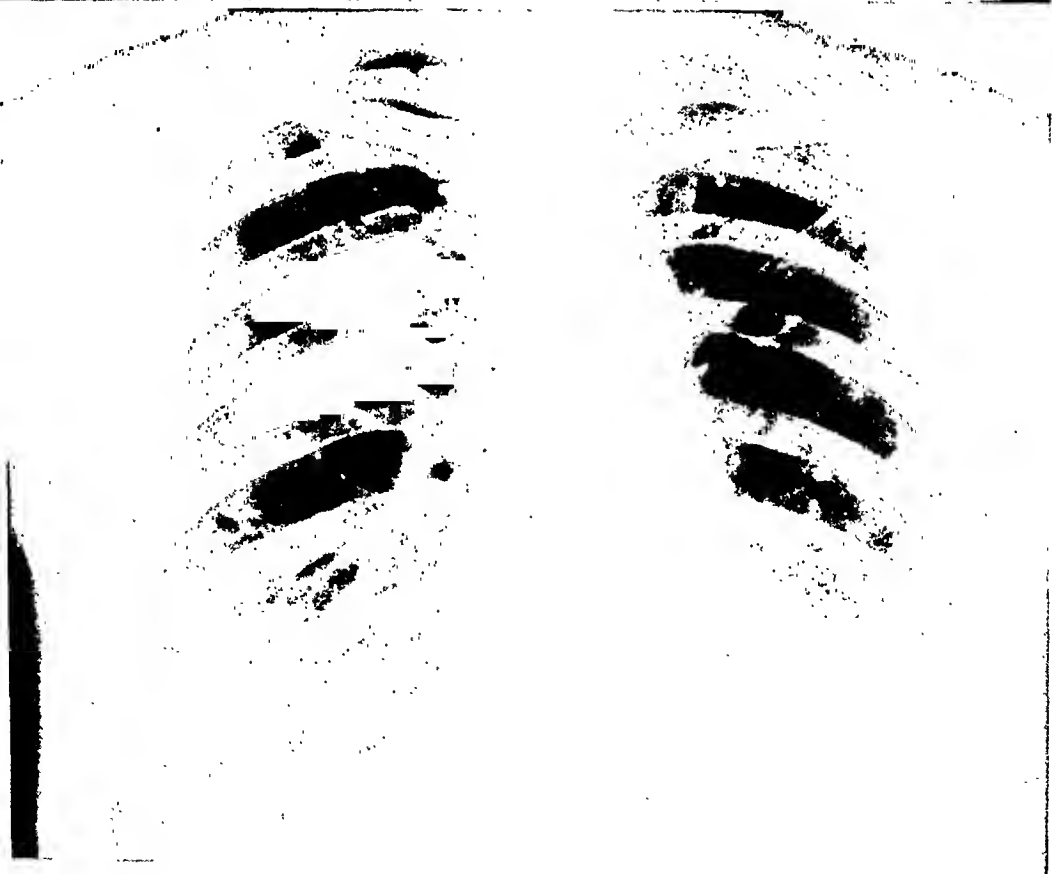
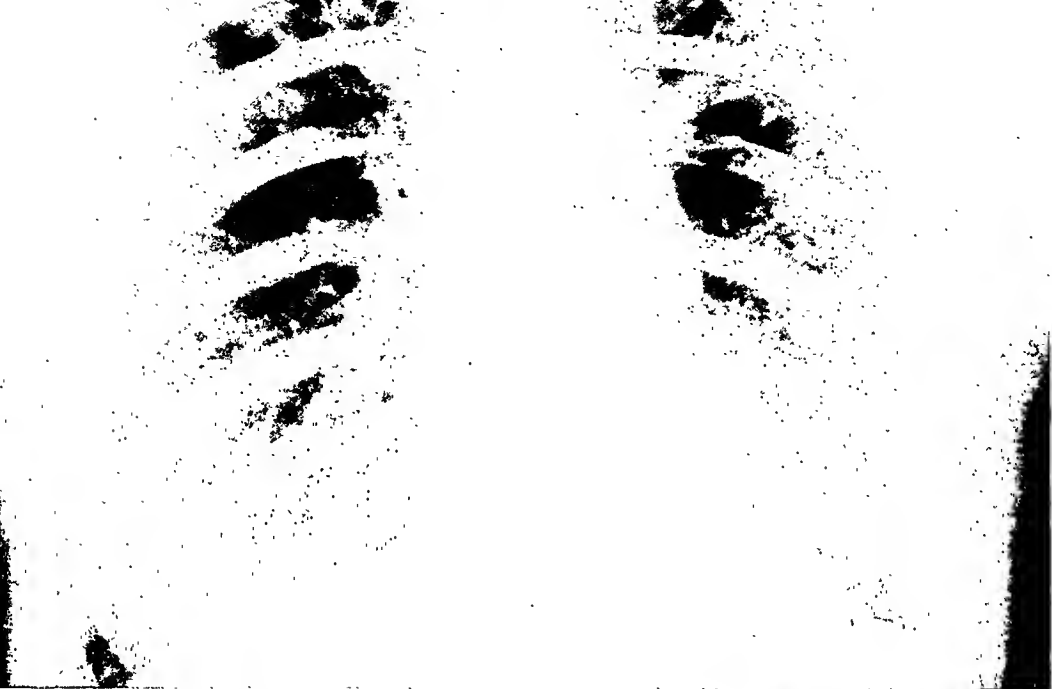


FIG. 6C. Case 6. August 9, 1947. Near end of streptomycin therapy.

FIG. 6D. Case 6. January 6, 1948. Six months after start (4½ months after end) of streptomycin therapy.

effects of the drug are well known (5, 6, 13, 14, 15). The most important manifestations observed among the twenty-six patients in the two principal categories of disease under consideration are listed in table 4.

Eosinophilia above 5 per cent was a common occurrence on regimen A; was rarely seen on regimen B. All patients were closely followed by audiometry and in no case was there any significant impairment of hearing. Renal function was

TABLE 3  
*Ulcerative tuberculous bronchitis in patients with disseminated  
or "grumbling" pulmonary tuberculosis*

| TYPE OF PULMONARY DISEASE | TOTAL PATIENTS | NUMBER BRONCHOSCOPED | NUMBER WITH ULCERATION | NUMBER HEALED | RELAPSE |
|---------------------------|----------------|----------------------|------------------------|---------------|---------|
| Disseminated.....         | 15             | 13                   | 7                      | 7             | 0       |
| "Grumblers".....          | 11             | 11                   | 3                      | 3             | 1       |

TABLE 4  
*Toxic reactions to streptomycin in "grumblers" and in patients  
with disseminated nodular pulmonary tuberculosis*

| DOSE REGIMEN                                  | TOTAL PATIENTS | SYMPTOMS OF LABYRINTH DYSFUNCTION |      |          |        | RESPONSE TO CALORIC STIMULATION AT END OF TREATMENT |                |             | RASHES           |         |
|---|----------------|-----------------------------------|------|----------|--------|---|----------------|-------------|------------------|---------|
|   |                | None                              | Mild | Moderate | Severe | Normal  | Hypo-sensitive | Insensitive | Acute with fever | Chronic |
| A. 1.5 or 2.0 grains daily for 120 days*..... | 10             | 0                                 | 3    | 4        | 3      | 0   | 0              | 10**        | 1                | 2       |
| B. 1.0 gram daily for 42 days...              | 16             | 12                                | 3    | 0        | 1      | 11  | 4***           | 1**         | 2                | 0       |
| Totals...                                     | 26             | 12                                | 6    | 4        | 4      | 11  | 4***           | 11**        | 3                | 2       |

\* In 1 patient (Case 2) streptomycin was stopped at 62 days because of chronic skin rash; in another (Case 3) streptomycin was continued for 150 days instead of 120 days.

\*\* These patients were still insensitive 8 months after the end of treatment.

\*\*\* Caloric response eventually became normal in all these patients 2 to 5 months after the end of treatment.

not significantly impaired as determined by blood nonprotein nitrogen and phenolsulfonphthalein excretion tests. Transient granular casts and occasional erythrocytes were commonly found in the urinary sediment of patients on regimen A, less frequently when regimen B was employed.

As symptoms of a disturbed labyrinth, such as ataxia and vertigo, are the most significant, it is of interest to report that all patients have noted diminution in severity of symptoms and some degree of compensation for loss of equilibrium in the months following streptomycin treatment. This has occurred despite a continued lack of response to caloric tests. Nevertheless, the seriousness of this dis-

turbance should not be minimized, especially in patients with disease which constitutes no immediate threat to life. It should be pointed out that eight of the eleven "grumblers" were on regimen B, which was noteworthy for the low incidence of toxic manifestations. The three "grumblers" on regimen A have, fortunately, made excellent compensation for their labyrinthine dysfunction.

*Resistant Strains of Tubercle Bacilli.*<sup>5</sup> The emergence, in many patients treated with streptomycin, of strains of tubercle bacilli highly resistant to the action of streptomycin *in vitro* has been reported by numerous investigators (2, 4, 8, 9, 16 to 22). A consistent correlation between *in vitro* resistance and the response of patients to treatment is difficult to establish, but there is considerable evidence, drawn from other patients in the present study (11), and from the reported observation of others (7, 16, 17), that streptomycin is very unlikely to exert a favorable effect on tuberculosis once resistant strains of bacilli are demonstrated by *in vitro* tests. The practical importance of this phenomenon is, therefore, apparent, especially in patients with subacute and chronic tuberculosis such as the ones reported here. In none of the group of "grumblers", for example, was the disease immediately life threatening. Hence the desirability of using streptomycin for these "grumblers" would be even more dubious than it is, if it were found that the particular treatment regimen employed resulted in a high incidence of patients with resistant organisms. Such a patient's infection might then be refractory to streptomycin in the event of a more urgent need at the time of some future exacerbation of disease.

Prior to treatment, tubercle bacilli from all patients were found highly sensitive to streptomycin *in vitro* (growth inhibited by 0.5 or 1.0 mcg. of streptomycin per cc. of culture medium). In the group of "grumblers", cultures were consistently negative after the first month of treatment in four patients; in the remaining seven patients, at least isolated positive cultures have occurred following the completion of treatment and have permitted the performance of sensitivity tests. In one patient slightly less sensitive organisms appeared (growth inhibited by 10 mcg. per cc. but not by 5.0 mcg. per cc.); in all the others, growth was still inhibited by 0.5 or 1.0 mcg. per cc. when the organisms were last tested.

In the group with subacute and chronic disseminated nodular lesions, all cultures were negative after three to five weeks of treatment in three patients, the last positive culture being still highly sensitive to streptomycin in all three. In twelve patients, at least one or more isolated positive cultures were obtained after treatment was completed and were tested. In six of these patients, organisms from all cultures still had growth inhibited by 0.5 or 1.0 mcg. of streptomy-

<sup>5</sup> Sensitivity determinations on tubercle bacilli isolated from our patients and cultured at Laurel Heights were made at the Yale School of Medicine by Doctors Joseph Sadusk and William Swift (18), and more recently by Dr. Fred Beardsley. At the Laurel Heights Sanatorium, all the extensive technical laboratory work required on patients under study was performed by Mr. John Vadney and Mr. Hilary Morris. At the Yale School of Medicine, sensitivity studies were carried out with the technical assistance of Miss Eleanora Falco and Mr. Adolph Maruschak. These sensitivity studies were aided by a grant from the Fluid Research Fund of the Yale School of Medicine.

cin per cc. In three patients one or more cultures contained organisms whose growth was inhibited by 5.0 but not by 1.0 meg. per cc; in two patients, one or more cultures contained organisms whose growth was inhibited by 10.0 but not by 5.0 meg. per cc.; in one patient organisms requiring more than 1,000 meg. per cc. to inhibit growth eventually appeared. This last patient's organisms were still sensitive to 1.0 meg. per cc. at the end of a forty-two day course of treatment; the emergence of the highly resistant strain was delayed, occurring thirty-two days later. All of the three patients who produced organisms requiring 10 meg. per cc. or more to inhibit growth had gross collateral cavitation when treatment was started. In two of these patients, all cavities closed during streptomycin treatment; in one spontaneously, in the other after thoracoplasty was performed. The patient who eventually produced bacilli resistant to 1,000 meg. per cc. still has persistent chronic cavity.

#### DISCUSSION

There is little doubt that in pulmonary tuberculosis really fresh acute exudative lesions show the most rapid and complete response to treatment with streptomycin. The mere acuteness of a lesion is, however, neither the only criterion, nor always the most important criterion, for judging the potential usefulness of this drug. In the writers' experience, for example, acute lesions have responded very poorly to streptomycin when they were of a type which was already progressing rapidly to extensive caseation. Furthermore, the difficult therapeutic problems which arise in a typical tuberculosis sanatorium more often concern patients with predominantly subacute or chronic disease.

In the present study of streptomycin in clinical tuberculosis, patients with certain types of subacute and chronic disease have been included. Of these, the two types which furnish the principal material for this report are:

(1) Chronically unstable tuberculosis of limited extent, which has continued to be active and to produce sputum positive for tubercle bacilli in spite of prolonged treatment by conventional methods. The chronically unstable course of disease in these patients cannot be adequately explained on the basis of persistent visible cavity or bronchoscopically visible endobronchial tuberculosis alone. This group of patients has been designated as "grumblers".

(2) Subacute and chronic disseminated nodular pulmonary tuberculosis, which has failed to respond to treatment by bed-rest.

In the group of "grumblers", there is no doubt that streptomycin has produced temporary improvement in most patients. The principal evidence of this is the reduction or elimination of tubercle bacilli in sputum and gastric contents. Response has not been uniform, however, and relapses have already been observed in a small group of patients. It is possible, theoretically, that the "grumbling" course of disease in these patients may have been caused by different factors (e.g., chronic endobronchial tuberculosis beyond the range of bronchoscopic vision, tubercular bronchiectasis, chronic small foci of caseation, chronic cavity too small to be successfully visualized in roentgenograms). If this is so, it is a reasonable theory that response to streptomycin may differ corre-

spondingly. This theory is reasonable because, in other patients, visible ulcerative endobronchial tuberculosis has responded extremely well to streptomycin, even when chronic, while chronic caseation and cavitation usually have not. The true value of streptomycin in patients of this type remains to be determined. In patients with such chronically unstable disease, a much longer period of study and of follow-up will be required before the wide use of streptomycin can be recommended for such patients.

Response of subacute and chronic disseminated nodular tuberculosis to streptomycin appears to be unequivocal and marked. While the number of treated cases on which this opinion is based is relatively small, the evidence of improvement with streptomycin (in a group in which no patient was improving previously) is uniformly apparent, and is usually very pronounced. Moreover, within the time limits during which these patients were observed, the older lesions responded as regularly, and, in several patients, almost as markedly, as the younger lesions. It appears, therefore, that disseminated nodular pulmonary tuberculosis, whether acute, subacute or chronic, must be added to the list of lesions observed to be highly susceptible to streptomycin.

The evidence available from this investigation suggests that streptomycin and continued bed-rest may be all that is needed to produce arrest of tuberculosis in many patients with these disseminated nodular infiltrations, provided collateral caseation or cavity does not exist. If collateral caseous or cavernous lesions do exist and make collapse therapy or resection desirable, streptomycin may be an extremely valuable adjunct by controlling the disseminated nodular component. For example, one patient had extensive cavitation in the right upper lobe, but was unsuitable for thoracoplasty because of extensive disseminated nodular infiltration in the opposite lung which did not respond to bed-rest. Thoracoplasty was performed uneventfully, beginning eight weeks after treatment with streptomycin was started, and produced successful collapse of cavity. The disseminated nodular infiltration cleared steadily during and after the operative stages. The patient is now clinically well, and sputum and gastric contents have been consistently negative for more than six months.

Among the patients treated in this study, the emergence of strains of tubercle bacilli highly resistant to streptomycin *in vitro* (uninhibited in cultures containing 10 mcg. of streptomycin per cc.) has occurred thus far in none of the group of "grumblers" and in none of the patients with disease exclusively of the subacute or chronic disseminated nodular type. This experience is in marked contrast to the experience in patients with caseous or cavernous disease, in whom the emergence of resistant strains has occurred in a significant number, even when streptomycin was administered for only forty-two days. Among the patients with disseminated nodular lesions, the only one who eventually produced strains uninhibited by 10 mcg. per cc. of streptomycin or less was a patient who also had persistent cavity. While this experience is based on a relatively small series of patients and may be the result purely of chance, it suggests that the risk of clinically significant drug fastness may well be much less in "grumblers", and in patients with disease exclusively of the disseminated nodular type, than

in patients with frank caseation or persistent cavity. Until evidence bearing on this question is far more adequate, however, it is obviously important to consider carefully before deciding to give streptomycin to a patient in either of these two categories before other suitable forms of treatment have clearly failed. A tendency to relapse is a well-known characteristic of chronic tuberculosis, and it must still be assumed tentatively that streptomycin resistant tubercle bacilli may emerge in any tuberculous patient treated with streptomycin. Chiefly for this reason it seems advisable at present to treat patients in these two categories for forty-two days only, on the assumption (not yet clearly proved by experience) that streptomycin resistant strains are likely to emerge less frequently. Also, in this limited experience, patients in these two categories have shown approximately as good a therapeutic response to 1.0 gram of streptomycin daily for forty-two days as to 1.8 or 2.0 grams daily for one hundred twenty days; and the toxicity of the smaller dose is decidedly less.

In patients with disseminated nodular disease who require major collapse therapy (or resection) for collateral cavity or caseous lesions, it is important that such a procedure be performed relatively early in the course of streptomycin therapy. Otherwise streptomycin resistance may occur and the benefits of the drug may be lost before collapse or resection is performed. From the present experience, it is believed that surgery may be started early with confidence that streptomycin is extremely likely to control successfully the disseminated nodular component.

#### SUMMARY

1. In a larger study of streptomycin in various types of clinical tuberculosis, certain patients with subacute and chronic disease have been included. This report is concerned with observations on these more chronic lesions.

2. There is evidence, in a very limited number of cases, that ulcerative lesions of the larynx and major bronchi respond very favorably to streptomycin, even when such lesions are chronic. Principally, perhaps, through an effect on lesions of the draining bronchus, streptomycin may also favorably influence "tension" cavities. Sustained cavity closure is, however, only occasionally achieved by streptomycin alone after bed-rest has failed.

3. A favorable effect of streptomycin has been observed in a group of patients with chronically active and unstable indolent pulmonary tuberculosis of limited extent and severity, which had not been arrested by long periods of treatment by conventional means. Patients in this group have been termed "grumblers". Results of streptomycin treatment are, however, not yet sufficiently consistent or definitive to justify wide use of streptomycin therapeutically in this group. Accurate evaluation will require more study and a longer period of observation after treatment.

4. Streptomycin exerted a consistent and marked effect in patients with subacute and chronic disseminated nodular pulmonary tuberculosis. Disease of this type appears to be highly susceptible to streptomycin.

## SUMARIO

*Tratamiento de la Tuberculosis con Estreptomicina*

1. En un estudio más extenso de la estreptomicina en varias formas de tuberculosis clínica, figuraban ciertos enfermos subagudos y crónicos. Este trabajo versa sobre las observaciones realizadas en esas lesiones más crónicas.

2. Hay pruebas, en un número limitadísimo de casos, de que las lesiones ulceradas de la laringe y los bronquios mayores, aun siendo crónicas, responden muy favorablemente a la estreptomicina. Principalmente, quizás, por su efecto sobre las lesiones del bronquio de desagüe, la estreptomicina puede también afectar favorablemente las cavernas de "tensión". Sin embargo, el cierre sostenido de las cavernas sólo de cuando en cuando lo logra la estreptomicina después de fracasar el reposo en cama.

3. Se ha observado efecto favorable de la estreptomicina en un grupo de enfermos con tuberculosis pulmonar indolente y crónicamente activa e inestable, limitada en su difusión y gravedad, que no había sido estacionada con prolongados períodos de tratamiento por los medios acostumbrados. A los enfermos de este grupo se les ha denominado "gruñones." No obstante, los resultados de la estreptomycinoterapia no son todavía suficientemente constantes o definitivos para justificar el empleo terapéutico de la estreptomicina en este grupo. La valuación exacta exigirá más estudio y un período más largo de observación postterapéutica.

4. La estreptomicina ejerció efecto constante y decidido en los enfermos con tuberculosis pulmonar ganglionar difusa, tanto subaguda como crónica. Esta forma de la enfermedad parece ser muy susceptible a la droga.

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## THORACOPLASTY OPERATIONS UNDER LOCAL AND REGIONAL ANESTHESIA

MANDEL WEINSTEIN<sup>1</sup>

Sufficient time has now elapsed to evaluate the results of local and regional anesthesia for surgery in pulmonary tuberculosis. At the time this method was first presented in 1938 (13), simple local infiltration anesthesia and paravertebral block anesthesia were used by some thoracic surgeons. Simple local anesthesia with novocaine has never produced enough anesthesia to permit a painless operation. Paravertebral anesthesia has been even less successful because its induction requires much experience. Besides, it must be supplemented by infiltrations locally. However, these types of anesthesia were always reserved for the "bad risk" patient, to whom inhalation anesthesia could not be given. In thoracic surgery, the general impression has prevailed that the operative area cannot be anesthetized sufficiently to permit a well planned thoracoplasty operation. The purpose of the present report is to review the results of the writer's method practised over a period of ten years, while at the same time recording modifications and additions to the technique previously described.

At the outset, it must be realized that to be successful any method of local anesthesia must be painless. Such anesthesia methods require even less tissue handling and trauma during the operation than when general anesthesia is being used. Even though pain, or the protopathic sense, is obliterated, touch and pressure or epicritic sensations may still be present. The persistence of touch and pressure sense results in the patient's feeling any tugging or pulling during the operation. Therefore, one must not only block pure sensory nerves, but also nerve fibers supplying all the muscles involved in the field of operation. Well relaxed muscles will result from such a procedure and exposure will be facilitated. All this causes a minimum of pain to the patient during the operation and creates good muscular relaxation, particularly for the removal of the upper ribs.

### ADVANTAGES OF LOCAL AND REGIONAL ANESTHESIA OVER INHALATION ANESTHESIA

Large quantities of inhalation anesthetic gases are not without harm in an already diseased and partly functionless lung parenchyma. Most tuberculosis patients are already overburdened with excessive secretion from tuberculous bronchitis, cavitated lung tissue, or bronchiectatic involvement of the lung. The ill effects of inhalation anesthetics are both local and general. The local effect of an anesthetic gas is one of irritation to these diseased tissues, and the production of an increased amount of tracheobronchial secretion. On the other hand, the general or systemic effect is a stagnation of secretions in the branches of the tracheobronchial tree. Deep surgical anesthesia suppresses bronchial muscular activity and retards ciliary action, thus preventing good bronchial drainage.

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The force of gravity when the head is lowered, and suction of the secretions by catheter, evacuate the secretions to some extent during general anaesthesia. Nevertheless, the absence of a good cough reflex, as in deep surgical anaesthesia, allows the spread of secretions from these puddles of purulent material to uninvolved lung areas. Such "spreads" account for the greatest morbidity and mortality in tuberculosis surgery.

Where general anaesthesia with an intratracheal catheter is used, much of this secretion may be aspirated by the anesthetist during the operation. Tuberculosis of the trachea and larynx is quite common, however, and there is a danger of local trauma from the use of a catheter. Moreover, patients with fibrotic lesions may present distorted and retracted tracheae, a condition that does not permit safe passage of the catheter.

Another good reason for the use of local anaesthesia in tuberculosis patients is that such patients have a lowered vital capacity and suffer from varying degrees of anoxia. Anoxic states particularly result from contralateral pneumothorax, extensive parenchymal involvement, phrenic nerve operations, secondary thoracoplasty operations, empyema, bronchiectasis, reexpanded lungs following pneumothorax, and emphysema. Again, the position on the operating table is in itself a factor limiting vital capacity. The operating position is the lateral recumbent one, with the good lung lying underneath, thus being compressed. The operated side is uppermost and is limited in its ventilation both by the patient's disease and by the operative trauma.

Unlike general anaesthesia, the patient remains conscious during local anaesthesia, and muscle tonus is still present in the muscles of respiration. This almost intact respiratory muscle action, by helping to maintain pulmonary inflation, prevents to some extent any further increase in the patient's anoxic state. Cyclopropane and other anesthetic gases, by permitting high percentages of oxygen, will also overcome anoxia. However, such anoxia returns when the oxygen is discontinued at the end of a general anaesthesia.

In brief, local and regional anaesthesia should be offered to all operative pulmonary tuberculosis patients as the anaesthesia of choice, and not alone to the "poor surgical risks". In addition, the following patients who ordinarily would not be operated upon may, in this manner, be given the opportunity of chest surgery: hypotensives and hypertensives; diabetic patients; those in the advanced age group; patients with extensive amyloid disease; and individuals in lowered states of nutrition.

#### DISTRIBUTION AND FUNCTION OF NERVES TO THE THORAX

The following discussion will be limited to those nerves supplying the regions of the thorax related to thoracoplasty procedures. Most of these are purely sensory nerves, but others must be blocked which innervate muscles to be incised in the operative field. Muscle tissue throughout the skeletal system contains sensory fibers termed neuromuscular endings or muscle spindles (9, 6). First described by Kolliker and by Kuhne, they are regarded as sensory endings, probably concerned in affording impressions as to tension, or "muscle sense"

(9). They lie within the connective tissue separating the bundles of voluntary muscle fibers. The sensory fibers are connected with the neuromuscular end organs or muscle spindles, from which the afferent nerves proceed centrally. As forcible retraction of the scapula is necessary, obtundation of muscular impulses permits free and easy exposure by relaxing the shoulder girdle muscles. The novocaine injections create a local infiltration and a regional intercostal nerve block on the posterior aspect of the thorax. To relax completely the muscles

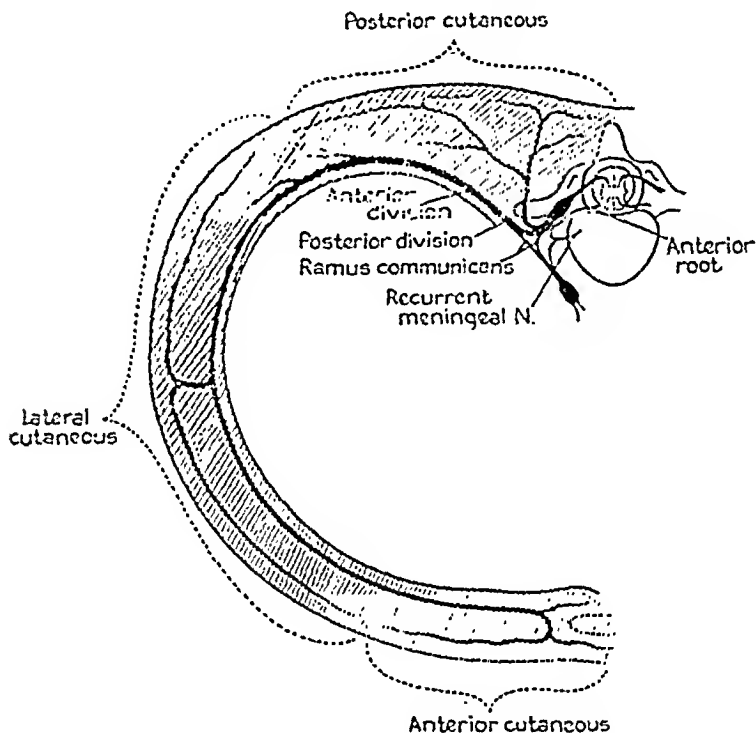


FIG. 1. A typical spinal nerve with special emphasis upon the sensory distribution to the thoracic wall.

attached to the scapula, the subscapular and long thoracic nerves must be blocked, and they are reached in the axilla.

The thoracic nerves (figures 1 and 2), are twelve in number and emerge through the intervertebral foramina midway between two transverse processes. Upon making its exit, each nerve divides into an anterior and a posterior primary division (7). The latter courses posteriorly to supply the muscles and integument of the chest, anteriorly, laterally, and posteriorly.

The subscapular nerves arise from the posterior cord and are usually three in number. They supply the three muscles forming the posterior boundary of the axillary space, namely, subscapularis, teres major, and latissimus dorsi. They are only blocked during a first stage thoracoplasty and contribute much to good anesthesia.

The upper (or short) subscapular nerve originates behind the circumflex nerve,



before operation, one Seconal tablet is given (0.1 gram). The morning of operation, two hours before going to the operating room, 0.180 gram of Sodium Amytal is given, followed one hour before operation by morphine sulphate, 0.015 gram, and scopolamine hydrobromide, 0.004 gram.

Of late, an important addition has been made to this method of anesthesia. At the start of the operation, sodium pentothal is given intravenously in a quantity sufficient to create analgesia but not anesthesia. The optimum dosage permits grunting and also coughing and coughing efforts. In this way the tracheobronchial tree remains a mobile structure that can prevent inundation of the smaller air passages by secretion. Two grams of sodium pentothal are added to 1,000 cc. of five per cent glucose in saline, and the solution is permitted to flow interruptedly into the vein in quantities sufficient to quiet the patient. A stopcock mechanism controls the amount of flow and shuts off the solution as soon as the patient manifests signs of becoming drowsy. When the patient becomes restless or too alert, the solution is again permitted to enter the vein. This interrupted method of administering the sodium pentothal is kept up throughout most of the operation. However, a poor local and regional anesthesia defeats the purpose as too large a quantity of sodium pentothal will be required. Not more than a total of two-thirds to 1.0 gram of the drug should be used. This is equivalent to 300 to 500 cc. of the solution. This amount of glucose in saline solution plus 1,000 cc. of blood is usually sufficient intravenous medication to last throughout the operation. A cannula is inserted into the internal saphenous vein at the ankle, thus assuring a continuous flow into the vein. A "Y" connecting glass tube, or a similar arrangement, permits the bottles of glucose solution and blood to flow into the vein singly or together. A continuous flow of oxygen is maintained while the patient is on the table, either with the mask of the usual anesthesia machines, or, better still, by means of a number 12 French nasal catheter. The distance from the nares to the external auditory meatus is measured and serves to indicate the depth in the nose to which the tip of the catheter should be inserted. Setting the oxygen reduction valve at four to five liters per minute will continuously deliver 40 to 50 per cent oxygen to the nasopharynx by this simple method. The catheter method is preferred because of the ease of administration and the avoidance of contaminating the machine.

Patience and dexterity in the insertion of the injecting needles contribute a large share toward good anesthesia. Needle points should be unusually sharp so that the operator can gauge the different degrees of resistance of the tissues while passing through varying depths. Deep fascia must always be palpated with the needle point before infiltrating underlying muscle. The direction of the needle should never be changed unless the point is in the loose subcutaneous tissue. Only in this manner can the angle be altered without the danger of breaking the shaft of the needle. Intracuticular wheals are to be made with the finest possible needle point and, if there is any indication of pain, that particular area must be rendered anesthetic before proceeding further.

As regards tissues, the skin is sensitive and the underlying deep fascia and fascia over muscles also occasionally give rise to a slight sensation of pain. Muscle tissue is not sensitive to pain unless retracted suddenly and roughly, but cutting through a sheet of muscle is sometimes accompanied by an unpleasant sensation as the fibers contract and wriggle away (12). Periosteum is acutely sensitive, and, due to the overlapping of nerve fibers, it is necessary to block one nerve above and one below the rib to be removed. Sectioning of ribs is actually painless if the anesthesia is good. Caution should be exercised during the handling of the heavy instruments so that pressure is not made upon the chest, or the patient "shaken" on the table. Even though pain is eliminated during

a perfect anesthesia, pressure and touch sense may still be present. The parietal and mediastinal pleurae are normally sensitive membranes, but, if anesthesia is complete, dissection of these structures gives no pain (Semb Decollation Technique).

The plan of the anesthesia is divided in two parts. First, an infiltration is made regionally in the axilla to block the long thoracic and subscapular nerves. These supply the latissimus dorsi, serratus anterior, and scapular muscles. Then the patient is draped in the usual manner, and the wound area is infiltrated. Only in a first-stage thoracoplasty is it necessary to block the nerves in the axilla, because of the necessity of relaxing the shoulder girdle muscles to reach the uppermost ribs. In second- and third-stage thoracoplasty operations, infiltration in and around the area of incision may be accomplished after the drapes are prepared for operation.

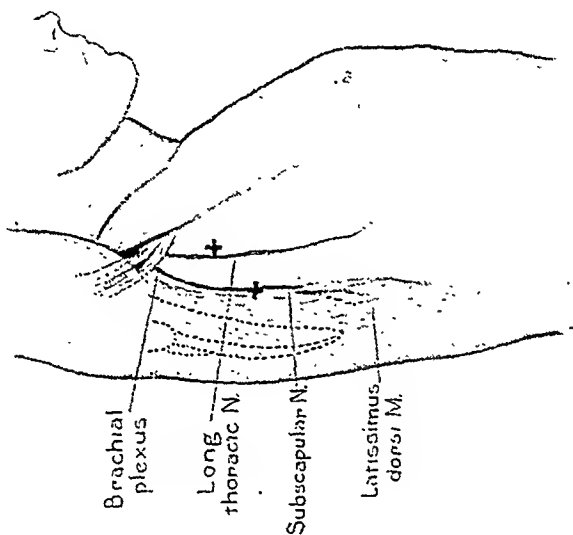


FIG. 3. A first stage thoracoplasty operation, preliminary to anesthetizing the operative area posteriorly. The needle passing through the upper point blocks the long thoracic nerve supplying the serratus anterior muscle. The postero-inferior point permits anesthetization of the three subscapular nerves supplying the subscapularis, teres major, and latissimus dorsi muscles.

**Upper Stage Thoracoplasty:** The anesthesia produced should be complete enough to permit removal of three or four upper ribs in full lengths, together with the tips of the transverse processes. In addition, it should be possible to remove the intercostal muscles, vessels, and nerves, and to perform the decollation procedure of Semb whenever indicated, with a resulting drop of the apex of the lung to the level of the fourth rib posteriorly.

Novocaine is used as the anesthetic drug in one per cent solution. Epinephrine (1:1,000) is added in the proportion of three drops to 30 cc. of novocaine, for a greater concentration induces rapid pulse, pallor, and the signs of oncoming shock.

The first part of the anesthetization is confined to the axilla, where injections are made of the long thoracic nerve (which supplies the serratus anterior) and the three subscapular nerves. Injection of the long subscapular nerve with novocaine anesthetizes and relaxes the latissimus dorsi muscle; and blocking of the impulses along the upper and lower subscapular nerves accomplishes the same for the subscapularis and teres major. Relaxation

of all these shoulder girdle muscles, together with the serratus anterior (which applies the scapula snugly to the chest wall), permits wide exposure for removal of the upper ribs when the scapula is retracted upward and outward.

With the patient lying on his opposite side, and prior to draping for operation, the arm is held upward and away from the chest exposing the inner wall of the axillary space. Here lie the digitations of the serratus anterior arising from the upper nine ribs. The long thoracic nerve lies on the lateral aspect of this muscle (figure 3). Palpating with the left index finger, the lateral surface of an uppermost rib at the midpoint of the axillary space is identified. An intradermal wheal is raised prior to the entrance of a three-inch needle. Contact is made directly with this rib. Continuing the use of the left index finger as a guide, fan-shaped injections of a one per cent novocaine solution are made along

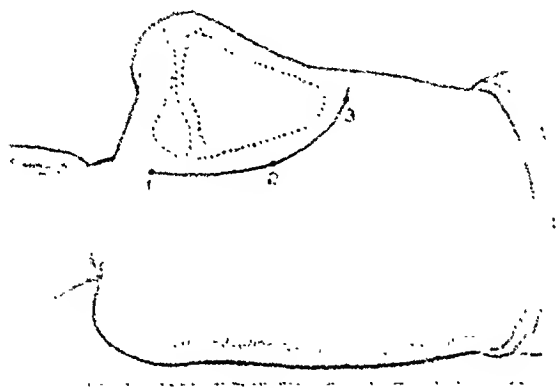


FIG. 4. Wheal is raised at point number 1, midway between the vertebral border of the scapula and the midspinal line, at the level of the upper scapula border. Point number 3 is 2 centimeters below the inferior angle of the scapula; and point number 2 is midway between both of these.

the outer surface of the rib anteriorly and posteriorly, the latter up to the scapula muscles. The solution infiltrates the nerve trunk, as well as the digitations of the muscle, with contained twigs that branch off at an upper level.

The long subscapular and the upper and lower subscapular nerves lying in the subscapular fossa are then blocked. The axillary border of the scapula is identified at about its middle and a wheal is raised just anterior to its midpoint. A long needle, about five inches in length, is advanced in a slightly upward direction to make contact first with the anterior surface of the bony scapula, in the subscapularis fossa. Then, two or three injections of novocaine, one per cent, are made into the subscapularis muscle itself, thus ensuring anesthesia of the fibers of the upper and lower subscapular nerves.

Forceful propulsion of the arm backward moves the scapula further away from the chest wall and aids exposure of the axillary space. Injury to the axillary vessels and nerves is possible but, with the arm extended and abducted, these structures recede from the chest wall and lie above and posteriorly, thus assuming a direction closer to the arm.

The operative area around the scapula is now prepared and properly draped, and the arm held slightly forward so as not to disturb the normal relationship of the scapula to the chest wall. Three wheals are raised with a fine intradermal needle through which a long fine three-inch needle distributes one per cent novocaine (figure 4). Wheal number one is placed midway between the scapula and midspinal line, on a level with the upper



scapular margin. Wheal number three is raised at a point two centimeters below the inferior angle of the scapula. Wheal number two is placed equidistant between one and three, while the surgeon bears in mind the curve to be described by the scapular incision. Points one, two and three are now connected in a curved manner with an intradermal infiltration, so that the future incision can extend from the level of the second dorsal spinous process to the middle axillary line. A corresponding anesthetization is made of the underlying subcutaneous tissue and musculature, the latter being injected last in a fan-shaped manner. It must be remembered that the muscles opposite the uppermost fourth and fifth ribs are very thick, and the infiltrating needle must pass deeply to anesthetize the entire extracostal muscle mass (1). Using a long needle and with proper precautions against penetrating into the pleural cavity, several fan-shaped injections may also be made anterior to and under the scapula, thus doubly ensuring painless retraction of the scapula.

The incision is now made through skin, subcutaneous tissue, and musculature, exposing the plane of the ribs. In this region it is now much easier to infiltrate the intercostal nerves after the intercostal spaces have been exposed. When attempting this, aspiration should be frequently done to avoid penetrating pleura and lung, as well as to avoid depositing a large amount of novocaine in an intercostal vessel. A fine, shorter needle carrying 2 per cent novocaine should be used for anesthetizing the nerves. The needle is passed through the lateral fibers of the sacrospinalis muscles. About 3 cc. of one per cent novocaine solution is deposited in the region of the posterior periosteum of each rib to be resected, at approximately two to three centimeters mesial to the angle. No attempt should be made to inject the nerve sheath far posteriorly, for fear of the solution being carried to the spine within the coverings of the cord which end in this location. The needle is then withdrawn and injected into the external intercostal muscle, making contact with the intercostal nerve. Three cc. of fluid are injected into this area. Posterior to the angles of the ribs, the nerves lie midway between two ribs and not in the subcostal groove. Here there is no internal intercostal muscle and the nerve lies between the posterior intercostal membrane and the external intercostal muscle.

Inasmuch as the third rib is removed first, and so on upward, the sequence of thoracic nerve injections should be from below upward. If the upper three ribs are to be resected, the fifth nerve should be injected in the beginning. However, it is easier to block the first intercostal nerve after the third and second ribs have already been removed. As stated previously, this method of anesthesia also allows a Semb decollation after the removal of ribs and intercostal bundles, without causing pain to the patient.

In a few cases before the development of this method of anesthesia, paravertebral block was tried in an attempt to infiltrate the nerves before making the incision. However, this procedure was found to be less accurate, more time-consuming and accompanied by less complete anesthesia. Opinions vary, as stated previously, as to the necessity of blocking the nerves in the axilla, for they are usually described as muscular branches. However, by completing the entire technique as above described, better anesthesia and more complete muscular relaxation have resulted. Fewer additional injections of novocaine into the tissues are required during the operation, and supplementary inhalation anesthesia never becomes necessary.

**Second and Third Stage Thoracoplasty:** After a first-stage thoracoplasty operation, fewer problems present themselves for inducing adequate anesthesia. All the tissues on the chest wall are less sensitive to pain stimuli than at the time of the first stage. Severed nerve fibers have produced large areas of anesthesia. The anatomical structure of the chest has been greatly altered with resultant muscular atrophy. There is diminished vascularization to the parts and abundant formation of cicatricial and fibrous tissue.

Moreover, the technique is more simplified because retraction of the scapula is practically unnecessary and the troublesome first rib has already been removed.

The line of incision is well infiltrated with one per cent novocaine and the intercostal nerves are injected in the usual manner, including at least one space above and below the ribs to be removed. If pain is experienced, especially anteriorly, while denuding and resecting the rib at its chondral junction, additional injections of novocaine may be made. The skin scar is always excised.

**Revision of Thoracoplasty:** A widespread local novocaine infiltration of the skin is produced, as well as the subcutaneous tissues and musculature, with one per cent novocaine. In addition, after making the incision by excising the scar, all the intercostal nerve regions are infiltrated in the same manner as previously described. Because of the marked distortion of the chest wall from previous operation, more difficulty is experienced in locating the thoracic nerve regions in the intercostal spaces posteriorly. The transverse processes and posterior rib stumps serve as guides for the regenerated intercostal nerves, the long stumps of severed intercostal nerves, and the intact intercostal nerves. The previously described method of infiltration of novocaine midway between the posterior portions of ribs gives excellent anesthesia for the revision operation.

**Complications and Dangers:** The induction of local and regional anesthesia with novocaine and epinephrine in chest surgery entails certain problems particular to this region. Special caution should be observed in regard to the amount of novocaine and epinephrine used, for the operative area is large in thoracic operations. In addition, it should be borne in mind that injections anywhere in the neighborhood of the lesser circulation may give rise to fatal air embolism.

**Novocaine and epinephrine toxicity:** Throughout all other regions of the body where surgical procedures are performed the question of such ill effects does not occur. This results from the fact that similar large quantities of these drugs are seldom required in order to obtain satisfactory anesthesia. In thoracoplasty surgery for pulmonary tuberculosis, the incision and subsequent operative steps cover a much larger anatomical field which requires more anesthetic drug and permits greater absorption. Moreover, according to Labat (7), the rate of absorption is unusually rapid on each side of the vertebral column. Where the drug is used regionally to block nerves, the only method of absorption is through the circulation. However, where local infiltration is resorted to, there is less danger from a large quantity of the anesthetic fluid in the tissues, as the incision and operative procedure permit a large amount to drain out of the wound during the operation.

The judicious use of epinephrine requires no comment and, if only 3 drops are added to 30 cc. of novocaine, there is little danger of overdosage. Epinephrine is valuable in preventing absorption of the novocaine systemically, thus prolonging its action locally. In addition, extensive tissue ischemia is produced in the fascial and muscular layers, thus obviating great blood volume loss and necessitating less clamping of bleeding vessels. In fact, when general anesthesia was used in the early days of thoracoplasty, it was the practice to inject a well diluted solution of epinephrine chloride into the tissues to prevent excessive bleeding (4).

Novocaine (procaine) was discovered by Braun (3) in 1905 and is one-third as effective and seven to ten times less toxic than cocaine (2). Watery solutions up to 10 per cent have little local irritating or toxic action on the tissues. It may be sterilized and resterilized by boiling without any marked effect upon its anesthetic properties. The solution becomes yellow when decomposed. It is the safest and best anesthetic for local infiltration. The addition of epinephrine in proportions of 3 drops to 30 cc. of novocaine doubles the intensity and quadruples the duration of the anesthesia.

As for the toxicity of novocaine, it should not be overlooked that large amounts are

in themselves toxic. Babcock (2) states that in the adult 500 cc. of a one per cent solution may be injected subcutaneously without evident toxic effect. For thoracoplasty operations, Alexander feels that 150 cc. of one-half per cent novocaine solution, and 30 cc. of one per cent solution is safe. Sauerbruch, who limits himself to 1.9 gram of novocaine has seen cases of dangerous collapse which he has attributed to novocaine (10). However, patients differ in their susceptibility to poisoning from the drug and no statement can be offered as to what is the maximum safe dose. The following must always be borne in mind: (1) untoward results when accidentally injecting into a vein or into the subdural space; (2) the toxicity resulting from a decomposed novocaine solution; and (3) "novocaine poisoning" due to the use of toxic doses of epinephrine. In case of severe local anesthetic poisoning, Emil Mayer recommends artificial respiration, cardiac massage, and the intracardiac injection of 2 cc. of one to ten thousand epinephrine solution through a needle six or seven centimeters long (8).

*Air Embolism:* This serious accident can usually be avoided by aspirating prior to injecting an anesthetic, whenever the needle is in proximity to the lung or pleura. The injection of air into the general circulation is usually devoid of any serious accident. Here the air is continually absorbed in its travel and, as the blood passes through the lungs, it is filtered out before it reaches the coronary or cranial arteries. The actual injection of air itself is not necessary to produce air embolism as the sucking action in the venous channels, due to the negative pressure of the pulmonary veins, may in itself introduce air into this system. Thence, the air travels to the left heart, coronary arteries, and cranial or other arteries.

Schlaepfer (11) found that death could be induced in a dog by the injection of as little as one cc. of air into the pulmonary vein. In cases in which there are adhesions between the lung and chest wall, small veins, which empty directly into tributaries of the pulmonary vein, are frequently present. Schlaepfer also clearly showed the importance of gravity in directing the air to the higher centers. If, after the injection of a small amount of air into the pulmonary vein, a dog was placed in a semi-erect position, air bubbles could be detected in the retinal vessels by ophthalmoscopic examination. Death occurred much sooner than if the animals were kept in a horizontal position. This indicates the importance of maintaining the head below the level of the pelvis during a thoracic operation. Occasionally the needle will penetrate directly into an alveolus or bronchiole without traumatizing a vein. In such instances there are no ill effects as the introduced air escapes up through the bronchial tree.

The symptoms vary with the location and multiplicity of the emboli. The air floats on top of the blood stream and the immediate effects may be convulsions, blindness, and positive findings in the retinal vessels. At the first indication of symptoms, the head should be lowered immediately, and cardiac stimulation given if necessary.

#### POSTOPERATIVE RESULTS IN 104 THORACOPLASTY OPERATIONS

In order to evaluate the advantages or disadvantages of local and regional anesthesia, a series of 104 thoracoplasty operations has been analyzed. The series includes all the private and ward patients operated upon by the writer during a ten year period at the four New York City hospitals enumerated in table 1. Hence, there is no artificial selection of cases and the types of operative procedures are essentially uniform, having been performed by the same operator. The type and extent of the tuberculosis among private and ward patients is the same and in New York City it is not at all uncommon to find private tuberculosis

patients who have been in the wards of charity hospitals, and vice versa. In addition, the same indications for operation apply to all patients, regardless of the institution. Fortunately for the purposes of this study, there has been an almost equal number of private and ward patients, and an almost equal division of operations under inhalation anesthesia, and local and regional anesthesia.

*Anesthesia:* In table 2 are listed the number of operations performed under inhalation anesthesia and under local and regional anesthesia.

There was an even distribution of these two types of anesthesia, as may be seen in table 2. Fifty were performed under inhalation and 54 under local and re-

TABLE 1  
*Total number of operations*

| HOSPITALS                        | PATIENTS | OPERATIONS—STAGES |     |     |     |          | TOTAL OPERATIONS |
|----------------------------------|----------|-------------------|-----|-----|-----|----------|------------------|
|                                  |          | 1st               | 2nd | 3rd | 4th | Revision |                  |
| Queens General.....              | 12       | 11                | 9   | 2   |     |          | 22               |
| Metropolitan.....                | 12       | 10                | 9   | 6   |     |          | 25               |
| St. John's Long Island City..... | 1        | 1                 | 1   |     |     |          | 2                |
| Boulevard.....                   | 26       | 26                | 24  | 3   | 1   | 1        | 55               |
| Total.....                       | 51       | 48                | 43  | 11  | 1   | 1        | 104              |

TABLE 2  
*Types of anesthesia*

|                                    | OPERATIONS—STAGES |     |     |     |          | TOTAL | PER CENT     |
|------------------------------------|-------------------|-----|-----|-----|----------|-------|--------------|
|                                    | 1st               | 2nd | 3rd | 4th | Revision |       |              |
| Inhalation.....                    | 22                | 20  | 8   |     |          | 50    | 48 per cent  |
| Local and regional anesthesia..... | 26                | 23  | 3   | 1   | 1        | 54    | 52 per cent  |
| Total.....                         | 48                | 43  | 11  | 1   | 1        | 104   | 100 per cent |

gional anesthesia. Even though the surgeon performs the local and regional block anesthesia, the services of a competent anesthetist are still required to administer sodium pentothal, to watch for incipient shock, and to supply oxygen for anoxia. Sodium pentothal has been added only during the past three to four years, or in approximately 25 per cent of the cases. Prior to that time, small doses of morphine sulphate were administered intravenously during the operation to relieve pain and to allay apprehension. However, the depressant effect of morphine upon the respiratory system has always made its use a therapeutic hazard.

*Inhalation anesthesia:* An analysis of the different types of inhalation anesthesia is presented in table 3. A subdivision of operations into the various stages of thoracoplasty, with the types of inhalation anesthesia used, is also included.

Cyclopropane anesthesia has been the most frequently used type of inhalation anesthesia in this series. An intratracheal catheter supplemented the procedure five times, or in 10 per cent of the operations. The indications for an intratracheal catheter have been the expectoration of more than one cup of sputum in twenty-four hours or the presence of a bronchopleural fistula with empyema. With the additional safeguard of a catheter, an attempt is made to avoid the spread of bronchial secretions to uninvolved lung parenchyma.

TABLE 3  
*Inhalation anesthesia*

| OPERATIONS                         | STAGES |     |     |     |          | TOTAL | PER CENT     |
|------------------------------------|--------|-----|-----|-----|----------|-------|--------------|
|                                    | 1st    | 2nd | 3rd | 4th | Revision |       |              |
| Cyclopropane.....                  | 17     | 18  | 7   |     |          | 42    | 84 per cent  |
| Cyclopropane plus intratracheal..  | 2      | 1   |     |     |          | 3     | 6 per cent   |
| Nitrous oxide.....                 | 3      |     |     |     |          | 3     | 6 per cent   |
| Nitrous oxide plus intratracheal.. |        | 1   | 1   |     |          | 2     | 4 per cent   |
| Total.....                         | 22     | 20  | 8   |     |          | 50    | 100 per cent |

TABLE 4  
*Shock*

| OPERATIONS                      | TOTAL | STAGES |     |     |     |          | TOTAL IN SHOCK | PER CENT (104 OPERATIONS) |
|---------------------------------|-------|--------|-----|-----|-----|----------|----------------|---------------------------|
|                                 |       | 1st    | 2nd | 3rd | 4th | Revision |                |                           |
| Inhalation anesthesia.....      | 50    | 3      | 8   | 2   |     |          | 13             | 12.5 per cent             |
| Local and regional anesthesia.. | 54    |        | 1   |     |     | 1        | 2              | 1.9 per cent              |
| Total.....                      | 104   | 3      | 9   | 2   |     | 1        | 15             | 14.4 per cent             |

*Shock:* Under local and regional block anesthesia, shock occurred only two times, or an incidence of only 1.9 per cent. Under inhalation anesthesia, thirteen instances of shock developed, or 12.5 per cent. A total of fifteen cases of shock (14.4 per cent) occurred with both types of anesthesia.

A patient was considered to be in shock if the systolic blood pressure dropped to below 85 mm. of mercury, and the diastolic to below 60 mm. of mercury, and remained stationary below these levels for several readings. An arbitrary value of this type had to be adopted as low blood pressure readings per se may have no special significance as to shock in thoracoplasty surgery. Many tuberculosis patients come to the operating room with low pressures, but none of the patients in the present series had a systolic pressure of less than 95 mm. of mercury. The anesthesia chart of the average patient in shock during or immediately after a thoracoplasty procedure showed a drop in blood pressure to 70 mm. of mercury systolic, and 40 mm. of mercury diastolic, where it was maintained at a fixed level for several readings.

*Intrabronchial "spreads"*: The instances of intrabronchial "spreads" were identified from progress notes of clinical findings, as well as roentgenographic evidence when no such infiltrations were visible before operation. Under inhalation anesthesia, eleven intrabronchial "spreads" occurred, while under local and regional anesthesia only two "spreads" were noted. The total incidence was thirteen "spreads" in 104 operations, or 12.5 per cent.

All "spreads" were contralateral and comprised mild, moderate and severe "spreads" (bilateral "spreads" included). The above findings are consistent with a previous report by Weinstein and Tyau (14). In an analysis of 198 thoracoplasty operations at Sea View Hospital performed during the year 1942,

TABLE 5  
*Intrabronchial "spreads"*

| OPERATIONS                      | TOTAL | STAGES |     |     |     |          | TOTAL SPREADS | PER CENT (104 OPERATIONS) |
|---------------------------------|-------|--------|-----|-----|-----|----------|---------------|---------------------------|
|                                 |       | 1st    | 2nd | 3rd | 4th | Revision |               |                           |
| Inhalation anesthesia.....      | 50    | 6      | 4   | 1   |     |          | 11            | 10.5 per cent             |
| Local and regional anesthesia.. | 54    | 1      | 1   |     |     |          | 2             | 2.0 per cent              |
| Total.....                      | 104   | 7      | 5   | 1   |     |          | 13            | 12.5 per cent             |

TABLE 6  
*Wound infections*

| OPERATIONS                      | TOTAL | STAGES |     |     |     |          | TOTAL INJECTIONS | PER CENT (104 OPERATIONS) |
|---------------------------------|-------|--------|-----|-----|-----|----------|------------------|---------------------------|
|                                 |       | 1st    | 2nd | 3rd | 4th | Revision |                  |                           |
| Inhalation anesthesia.....      | 50    | 8      | 7   | 2   |     |          | 17               | 16.3 per cent             |
| Local and regional anesthesia.. | 54    | 2      | 1   |     |     |          | 3                | 2.8 per cent              |
| Total.....                      | 104   | 10     | 8   | 2   |     |          | 20               | 19.1 per cent             |

twelve local and regional anesthetics were done. Of these, only one "spread" occurred, and that one in a patient upon whom several attempts had been made preoperatively to pass an intratracheal tube under local anesthesia. Local and regional anesthesia was decided upon only after failure to pass the intratracheal tube. All twelve local and regional anesthetics in the aforementioned report were chosen for "poor risk" patients.

*Wound infections*: The diminished bleeding in local and regional block anesthesia contributed to the low incidence of wound infection. The local ischemic effect of novocaine and epinephrine infiltrating the tissues under pressure caused fewer extravasations of blood postoperatively. Moreover, as shock was more evident under inhalation anesthesia, delayed or secondary bleeding and oozing created collections of serosanguinous material upon the rise of the patient's blood pressure. Under the falling pressures of shock, a blood vessel that ordi-

narily would be clamped and ligated may not be visible, while under local anesthesia such patent vessels are seldom overlooked.

There were seventeen cases of infection after inhalation anesthesia and three cases of infection under local and regional. Thus, approximately five times as many wound infections were observed under inhalation anesthesia as under local and regional. Any type of wound drainage associated with fever was considered to be an infection, whether the fluid was serosanguinous, seropurulent, or purulent.

TABLE 7

*Mortality*

| OPERATIONS                      | TOTAL | STAGES |     |     |     |           | TOTAL MOR-TALITY | PER CENT (104 OPERATIONS) |
|---------------------------------|-------|--------|-----|-----|-----|-----------|------------------|---------------------------|
|                                 |       | 1st    | 2nd | 3rd | 4th | Revi-sion |                  |                           |
| Inhalation anesthesia.....      | 50    | 3      | 2   |     |     |           | 5                | 4.8 per cent              |
| Local and regional anesthesia.. | 54    | 2      | 1   |     |     |           | 3                | 2.9 per cent              |
| Total.....                      | 104   | 5      | 3   |     |     |           | 8                | 7.7 per cent              |

TABLE 8

*Inhalation anesthesia mortality*

| NUMBER | PATIENT | STAGE           | DEATH POST-OPERATIVELY | CAUSES OF DEATH                              |
|--------|---------|-----------------|------------------------|--|
| 1      | L. P.   | 1st             | 28 days                | Pulmonary embolism (postmortem)              |
| 2      | E. H.   | 2nd             | 12 days                | Spontaneous pneumothorax, contralateral lung |
| 3      | W. C.   | 1st             | 18 days                | Intrabronchial "spread"                      |
| 4      | G. B.   | 2nd plus Schede | 32 days                | Bronchopleural fistula and "spread"          |
| 5      | J. H.   | 1st             | 2 days                 | "Spread"                                     |

*Mortality:* In the early years, only the "poor risk" patients were given local and regional anesthesia. However, more recently all patients have been administered this type of anesthesia routinely. It would be proper to state that many of the patients in the series, who were operated upon as private patients under local and regional anesthesia, were referred by phthisiologists with the express purpose of avoiding inhalation anesthesia in "poor risk" and desperately ill patients.

There were eight deaths resulting from 104 operations, or an over-all operation mortality of 7.7 per cent, as noted in table 7.

In tables 8 and 9 are listed the individual causes of death. A case of pulmonary embolism occurred twenty-eight days after an inhalation anesthesia, and this obviously cannot be directly attributed to this particular method of anesthesia. At autopsy, an infarct, and a large cavity were found in the contralateral lung. A thrombophlebitic calf vein was discovered as the cause of the

trouble. Another instance of pulmonary embolism occurred in a patient operated upon under local and regional anesthesia. Even though a postmortem examination was not performed, the clinical findings seemed to be conclusive. Another patient, Mr. S. F., who died six days after a first stage thoracoplasty operation, was extremely ill with extensive cavitated lung tissue and a putrid empyema. There was an open bronchiopleural fistula with the almost continuous expectoration of foul pus. A thoracotomy tube was first inserted to decompress the putrid empyema, and four days later a first stage thoracoplasty was done under local and regional anesthesia. However, the drainage from the large patent fistula into the bronchial tree was so marked that an extensive bilateral "spread" resulted. This was the only death from an intrabronchial

TABLE 9  
*Local and regional anesthesia mortality*

| NUMBER | PATIENT | STAGE | DEATH POST-OPERATIVELY | CAUSES OF DEATH                             |
|--------|---------|-------|------------------------|---|
| 1      | T. T.   | 2nd   | 1 day                  | Pulmonary embolism                          |
| 2      | L. G.   | 1st   | 8 days                 | Unknown                                     |
| 3      | S. F.   | 1st   | 6 days                 | Putrid empyema; open fistula. Severe spread |

"spread" in the local and regional anesthesia group of cases, while under inhalation anesthesia there were four deaths from "spreads."

#### SUMMARY

1. Favorable results with local and regional anesthesia in thoracoplasty operations over a period of ten years suggest that this type of anesthesia be used as the method of choice in all cases and not merely for "poor risk patients."

2. The foregoing method of anesthesia may also be used to advantage and with safety in institutions where trained anesthesiologists are unavailable.

3. Under this method a patient, conscious throughout the operation, is able to cough and empty his bronchial tree and consequently leaves the operating table with very little shock and anoxia. There is less blood loss throughout the operation and fewer bronchogenic "spreads" postoperatively.

4. Special indications for local and regional anesthesia are: extensive bronchiectasis; tracheobronchial tuberculosis; tuberculous empyema and bronchiopleural fistulae; anoxic patients with low vital capacity; hypertensives and hypotensives; amyloid disease; lowered nutritional states; and patients in the advanced age group.

5. An interrupted intravenous flow of two-tenths per cent sodium pentothal solution throughout the operation prevents restlessness and allays apprehension while still permitting the patient to utilize the cough reflex.

6. A critical analysis of postoperative results in 104 thoracoplasty operations shows that local and regional anesthesia causes less shock, fewer intrabronchial spreads, less frequent wound infection, and fewer deaths. These conclusions are based upon a comparison of results in a series of 50 operations under inhala-



tion anesthesia with another series of 54 operations under local and regional anesthesia. An unselected group of private and ward patients in four New York City hospitals forms the basis of this study.

7. This type of anesthesia requires patience, skill, and the gentle handling of tissues to obtain the best results.

#### SUMARIO

##### *Toracoplastias con Anestesia Local y Regional*

1. Los resultados favorables obtenidos con la anestesia local y regional en las toracoplastias ejecutadas durante un decenio sugieren el empleo de esta forma de anestesia como técnica de elección en todos los casos y no puramente en los enfermos considerados como "malos riesgos."

2. Puede también utilizarse dicha anestesia con provecho e inocuidad en las instituciones que no cuentan con anesthesiólogos adiestrados.

3. Con dicha técnica, un enfermo, consciente durante toda la operación, tosiendo y vaciando su árbol bronquial, abandona la mesa de operaciones con muy poco choque y anoxia. Además, hay menos pérdida de sangre durante la intervención y menos propagación broncogénica postoperatoriamente.

4. Una indicación especial para esta clase de anestesia radica en: bronquiectasia extensa; tuberculosis traqueobronquial; empiema y fístulas broncopleurales tuberculosos; anoxia con poca capacidad vital; hipertensión e hipotensión; deficiencias nutritivas, tales como avitaminosis y flacura exagerada; y enfermos de edad avanzada.

5. Una corriente endovenosa interrumpida de solución de pentotal sódico al 0.2 por ciento durante toda la operación evita la inquietud y calma la aprensión a la vez que permite al enfermo utilizar el reflejo béquico.

6. El estudio analítico de los resultados postoperatorios en 104 toracoplastias demuestra que la anestesia local y regional ocasiona menos choque, más pocas propagaciones intrabronquiales, menos frecuente infección de heridas y menor mortalidad. Estas conclusiones se basan en la comparación de los resultados obtenidos en una serie de 50 operaciones verificadas con anestesia por inhalación y en otra serie de 54 operaciones con anestesia local y regional. Un grupo tomado al azar de enfermos particulares y de sala de cuatro hospitales de la ciudad de Nueva York forma la base de este estudio.

7. Esta clase de anestesia exige paciencia, destreza y manipulación delicada de los tejidos a fin de conseguir el resultado óptimo.

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## CAVERNOSTOMY

EDWARD ERNEST ROCKEY, SAMUEL ALCOTT THOMPSON, AND  
IRVING SHINER

Cavernostomy is an open drainage of a tuberculous cavity. The procedure is not new (1, 2, 3), but it has been modified by many thoracic surgeons. As many patients subjected to the procedure present individual surgical problems which require an appreciation of the pathophysiology of the lung, it is believed to be worth while to report a series of cases in which these factors are considered.

### CLINICAL MATERIAL

The present study deals with 22 cases operated upon at the Metropolitan Hospital from March 1942 to June 1947, inclusive (table 1). Nine patients were Negroes and 13 were white. Ten of the series were males and 12 were females. The age of the patients ranged from 18 to 53 years with a mean age of 35 years. It is difficult to tabulate the patients as a group, as each one of them presents individual features. However, an attempt is made to place them in an acceptable classification (table 2). All had far advanced pulmonary tuberculosis. Twenty-one patients had bilateral disease and only one had unilateral disease. Ten patients had active disease on both sides, the other 12 had active disease only on the operated side at the time cavernostomy was performed. All of the patients had received treatment for one to fourteen years prior to the cavernostomy. During this period of treatment the usual forms of therapy were tried, as may be seen in the individual case histories. The postoperative follow-up of these cases ranges from three to sixty-three months. The first patient in the series was operated upon in March 1942 and the last one in April 1947. Ten of the patients are dead and 12 are alive. The status of all patients was reviewed in May or June 1947. The extent and character of the disease which most of these patients presented made their outlook grave. However, 12 of them are alive, representing a 54.5 per cent survival.

### PROCEDURE

Cavernostomy is performed by the writers in one or two stages, depending upon the status of the lung tissue and pleura overlying the cavity. If the overlying lung tissue is atelectatic and the pleural layers are fused, the operation can be performed in one stage as was done in 10 of the present series. If the pleural layers are not adherent, the wound is packed with washed iodoform gauze for one week, after which time the cavity is opened at a second-stage operation, as was done in 12 of the series. The cavity should be carefully localized with the help of postero-anterior and lateral films, as well as fluoroscopic examination in the same position in which the patient is to be placed on the operating table. Tomograms are also helpful in the localization of the lesion. The overlying skin area can be marked with intradermal injection of methylene blue or by other means. The overlying ribs are removed by the extrapleural, subperiosteal method. The intercostal bundles overlying the cavity are excised and the cavity is unroofed as widely as

possible. The approach may be anterior, posterior, or lateral, but should be wherever the cavity is nearest to the chest wall. In the present series, the operative approach was anterior in 10, posterior in 10, and lateral in 2. In 10 of the cases, skin flaps (table 3) were formed and turned into the wound during the first stage. The tip ends of these flaps were attached to the parietal pleura or, if the cavity was opened during the first stage, the flaps were attached to the cavity wall. The purpose of these skin flaps is to keep the wound open, as well as to aid epithelialization of the cavity wall after its caseous layer has sloughed out. A number of the patients with controlled disease underwent secondary operations, such as skin flaps or skin grafts, in order to epithelialize the clean cavity wall. The open cavities are handled as any other dirty wounds. They were dressed daily or every second day, depending upon the amount and character of the discharge. Sulfonamide powder has been used locally to aid in keeping the wound clean. Systemic penicillin was also used during the first two or three weeks after operation in the cases which were operated upon during the past two years.

### RESULTS

There is a striking difference in the result of the cases with bilateral active disease as compared to the ones with active disease limited to the operated side (table 4). Ten of the cases had active disease in both lungs; 6 are dead and 4 are alive. Of the 4 living patients, only one is well in the sense that the pulmonary disease is controlled, the sputum contains no tubercle bacilli, and the wound is healed. One patient is classified as clinically improved, meaning that the disease is probably controlled, the discharge of tubercle bacilli in the sputum is intermittent, and the wound is clean and healing. Two patients are classified as unimproved or progressing, meaning that their pulmonary disease has remained unchanged or increased in extent, and they continue to discharge tubercle bacilli in the sputum. It is important to note that, clinically, even these patients showed improvement in that their expectoration decreased, appetite improved, and their general feeling was better. In the 12 cases with unilateral active disease, only 4 are dead. Of the 8 living patients, 4 are well with the disease controlled, wounds clean or healed, and no tubercle bacilli demonstrable in the sputum. Four of these patients are clinically improved with the pulmonary disease probably controlled, and tubercle bacilli are discharged in the sputum only occasionally.

A total of 5 of the 12 living patients were discharged from the hospital (table 5). This does not include one patient (S. R.) who was discharged in a condition which was classified "well" and died in another institution of what was considered to be cerebral tuberculosis. Four of the discharged patients are considered to be well, with their disease controlled and their wounds clean or healed. One of these patients was considered to be only clinically improved at the time of his discharge, as he still had active disease and discharged tubercle bacilli in the sputum. Nevertheless, his cavernostomy wound healed over completely about a year and a half after the operation and he is still clinically well forty-nine months after the operation. Seven of the living cases are still in the Metropolitan Hospital. One of these is well, with her pulmonary disease controlled, sputum negative for tubercle bacilli, and her wound clean. Four of these

TABLE 1  
Summary of 22 cases with cavernostomies

| NAME    | AGE<br>yrs. | SEX | DIAGNOSIS   | V.C., %<br>OF NORM. | DATE AND TYPE OF<br>OPERATION                                | HOSPITAL STATUS                   |   |                | SPTUM | RESULTS                              |
|---------|-------------|-----|---|---------------------|--|-----------------------------------|---|----------------|-------|--------------------------------------|
|         |             |     |   |                     |  | Discharged                        | Died  | Still in hosp. |       |                                      |
| 1 M. S. | 26          | F   | Bilat. far. ad-<br>vanced pulm.<br>tbc., both sides<br>active         | 32                  | 3-9-42 and 3-16-42,<br>two stage poste-<br>rior cavernostomy | 6-27-44, both<br>sides controlled |   |                | Neg.  | Asymptomatic,<br>returned to<br>work |
| 2 J. M. | 40          | F   | Bilat. far ad-<br>vanced pulm.<br>tbc., contralat.<br>side controlled | 37                  | 6-15-42 one stage<br>anterior cavern-<br>ostomy              | 3-1-44, both sides<br>controlled  |   |                | Neg.  | Asymptomatic,<br>returned to<br>work |
| 3 F. V. | 33          | F   | Bilat. far ad-<br>vanced pulm.<br>tbc., both sides<br>active          | 46                  | 9-28-42 one stage<br>lateral cavern-<br>ostomy               |                                   | 2-10-43, disease<br>progressive,<br>died of respir-<br>atory failure                        |                | Pos.  |                                      |
| 4 A. S. | 37          | F   | Bilat. far ad-<br>vanced pulm.<br>tbc., contralat.<br>side controlled | 42                  | 11-19-42 one stage<br>anterior cavern-<br>ostomy             | 2-8-45, both sides<br>controlled  |   |                | Neg.  | Asymptomatic,<br>returned to<br>work |
| 5 S. S. | 42          | M   | Bilat. far ad-<br>vanced pulm.<br>tbc., both sides<br>active          | 55                  | 3-11-43 one stage<br>anterior cavern-<br>ostomy              |                                   | 7-6-43, died of<br>tubercul. peri-<br>tonitis and kid-<br>ney sputum neg.                   |                | Neg.  |                                      |
| 6 S. M. | 23          | M   | Bilat. far ad-<br>vanced pulm.<br>tbc., both sides<br>active          | 41                  | 4-15-43 one stage<br>anterior cavern-<br>ostomy              |                                   | 5-22-44, died of<br>pulmonary<br>hemorrhage fol-<br>lowing second<br>stage thora-<br>plasty |                | Pos.  |                                      |

| B. M. | W     | 32   | M | Bilat. far advanced pulm. tbc., contralat. side controlled | 45        | 6-24-43 one stage posterior cavernostomy                        | 2-8-44, wound clean not controlled, has active pericavitary disease | 7-8-43, died of progression of the disease                              | Pos. | Clinically improved            |
|-------|-------|------|---|--|-----------|---|---|---|------|--------------------------------|
| 7     |       |      |   |  |           |   |   |   |      |                                |
| 8     | S. C. | W 51 | M | Bilat. far advanced pulm. tbc., both sides active          | 41        | 5-20-43 one stage anterior cavernostomy                         |   |   | Pos. |                                |
| 9     | E. K. | W 39 | F | Bilat. far advanced pulm. tbc., contralat. side controlled | 36        | 6-3-43 one stage posterior cavernostomy                         |   | 6-20-43, died of tuberculous nephritis. Sputum negative                 | Neg. |                                |
| 10    | G. R. | C 45 | M | Bilat. far advanced pulm. tbc., contralat. side controlled | 45        | 6-24-43 one stage anterior cavernostomy                         |   | 7-2-43, died of progression of the disease                              | Pos. |                                |
| 11    | S. R. | C 37 | F | Bilat. far advanced pulm. tbc., contralat. side controlled | No record | 10-16-44 one stage posterior cavernostomy                       | 1-3-45, sent to B.H. because of psychosis                           |   | Neg. | Died of cerebral involvement   |
| 12    | R. R. | C 31 | M | Bilat. far advanced pulm. tbc., both sides active          | No record | 9-17-45 and 10-1-45 two stage anterior cavernostomy             |   |   | Pos. | Sputa pos. disease progressing |
| 13    | H. T. | C 31 | M | Bilat. far advanced pulm. tbc., both sides active          | 39        | 9-30-45 and 10-14-45 two stage posterior skin flap cavernostomy |   |   | Pos. | Sputa pos. Disease progressing |
| 14    | H. H. | W 36 | M | Bilat. far advanced pulm. tbc., contralat. side controlled | 34        | 8-13-45 and 8-20-45 two stage anterior cavernostomy             |   | 11-2-45, died of air embolism following a dressing three months postop. | Neg. |                                |
| 15    | E. C. | C 41 | M | Bilat. far advanced pulm. tbc., both sides active          | 47        | 10-22-45 and 11-5-45 two stage lateral skin flap cavernostomy   |   | 3-19-46, died of progressive pulmonary disease                          | Pos. |                                |

TABLE 1—concluded

| NAME     | AGE | SEX | DIAGNOSIS   | V.C., %<br>OF NORMAL | DATE AND TYPE OF<br>OPERATION                                   | HOSPITAL STATUS               |  |  | SPUTUM | RESULTS                        |
|----------|-----|-----|---|----------------------|---|-------------------------------|--|--|--------|--------------------------------|
|          |     |     |   |                      |   | Discharged                    | Died   | Still in hosp.   |        |                                |
| 16 W. H. | 53  | M   | Bilat. far advanced pulm. tbc., contralat. side controlled                            | 49                   | 11-19-45 and 12-2-45 two stage anterior skin flap cavernostomy  |                               |  | Sputa alternately positive and neg. has large amount of pericavitary disease | Pos.   | Clinically improved            |
| 17 R. C. | 24  | F   | Bilat. far advanced pulm. tbc., both sides active                                     | 45                   | 12-17-45 and 1-7-46 two stage posterior skin flap cavernostomy  |                               |  | Cavity clean, has contralateral spread, pneumothorax instituted              | Pos.   | Clinically improved            |
| 18 T. N. | 18  | F   | Bilat. far advanced pulm. tbc., both sides active                                     | 38                   | 3-25-46 and 4-1-46 two stage posterior skin flap cavernostomy   | 6-7-47, both sides controlled |  |  | Neg.   | Asymptomatic, returned to work |
| 19 R. D. | 20  | F   | Bilat. far advanced pulm. tbc., both sides active                                     | No record            | 7-22-46 and 8-5-46 two stage posterior skin flap cavernostomy   |                               | 2-12-47, died of progressive pulmonary disease |  | Pos.   |                                |
| 20 M. C. | 39  | F   | Bilat. far advanced pulm. tbc., contralat. side probably controlled with pneumothorax | 53                   | 9-25-46 and 10-7-46 two stage anterior skin flap cavernostomy   |                               |  | Sputa alternately positive and negative                                      | Pos.   | Clinically improved            |
| 21 L. M. | 36  | F   | Far advanced unilateral pulm. tbc., post thoracoplasty case                           | 57                   | 11-14-46 and 12-9-46 two stage posterior skin flap cavernostomy |                               |  | Wound clean, sputa alternately positive and negative                         | Pos.   | Clinically improved            |
| 22 A. F. | 33  | F   | Bilat. far advanced pulm. tbc., contralat. side controlled                            | 48                   | 4-7-47 and 4-21-47 two stage posterior skin flap cavernostomy   |                               |  | Wound clean, sputa negative  | Neg.   | Well                           |

patients are considered clinically improved, with their pulmonary disease apparently stationary, wounds fairly clean, and sputum examinations occasionally

TABLE 2  
*Extent of pathology*

|  |    |
|--|----|
| Bilateral far advanced pulmonary tuberculosis, active on both sides..... | 10 |
| Bilateral far advanced pulmonary tuberculosis, one side active.....      | 11 |
| Unilateral far advanced pulmonary tuberculosis, active.....              | 1  |
| Total.....   | 22 |

TABLE 3  
*Type of operations*

|                        | TOTAL | DIED | ALIVE |
|------------------------|-------|------|-------|
| With skin flap.....    | 10    | 3    | 7     |
| Without skin flap..... | 12    | 7    | 5     |
| Total.....             | 22    | 10   | 12    |

TABLE 4  
*Results*

|  | TOTAL | DEAD | ALIVE | STATUS |             |              |
|--|-------|------|-------|--------|-------------|--------------|
|  |       |      |       | Well   | Clin. impr. | Pro-gressing |
| Bilat. far advanced pulm. tbc., both sides active                              | 10    | 6    | 4     | 1      | 1           | 2            |
| Bilat. far advanced pulm. tbc., one side controlled or unilateral disease..... | 12    | 4    | 8     | 4      | 4           | —            |
| Total.....   | 22    | 10   | 12    | 5      | 5           | 2            |

TABLE 5  
*Status of living patients*

|                        | TOTAL | WELL | CLINICALLY IMPROVED | PROGRESSING |
|------------------------|-------|------|---------------------|-------------|
| Discharged.....        | 5     | 4    | 1                   | —           |
| Still in hospital..... | 7     | 1    | 4                   | 2           |
| Total.....             | 12    | 5    | 5                   | 2           |

Seven out of the twelve living patients have bronchocutaneous fistulae.

positive for tubercle bacilli. Two are considered to be progressing because their pulmonary disease has spread to the same or the contralateral side and tubercle bacilli are easily demonstrable in the sputum. Clinically, even this group of patients seemed to have benefited somewhat from the procedure.



Analysis of the 10 deaths (table 6) shows that 5 died of progression of the pulmonary disease. Two patients died of intestinal and kidney involvement, one of air embolism, and one of pulmonary hemorrhage. One of the patients (S. R.) was discharged with a diagnosis of psychosis and her pulmonary disease controlled. She was classified as falling into the "well" group, but she subsequently died of what was considered to be cerebral tuberculosis. It is of interest to note that the 2 patients who died of kidney and intestinal involvement, as well as the one who died of air embolism, all had sputum which revealed no tubercle bacilli, and clean operative wounds, at the time of death. In other words, the status of their pulmonary disease was as satisfactory as the patients who are "well" to date. The death of the patient from air embolism occurred eighty-two days following the operation, shortly after the removal of the dressing

TABLE 6  
*Analysis of deaths*

|  |    |
|--|----|
| Progression of pulmonary disease.....  | 5  |
| Intestinal and kidney involvement.....   | 2  |
| Pulmonary hemorrhage.....  | 1  |
| Air embolism.....  | 1  |
| After discharge in a condition considered "well" died of cerebral involvement..... | 1  |
| Total.....   | 10 |
| Early operative death, 8 to 17 days postoperative.....                             | 2  |
| Late operative death, 49 to 413 days postoperative.....                            | 8  |
| Total.....   | 10 |

from his wound. This is the only air embolism encountered in the writers' experience or in the reviewed literature. The patient who died of pulmonary hemorrhage lived 413 days following his cavernostomy and the fatal hemorrhage occurred during a secondary thoracoplasty.

The following case records illustrate the various types of pathology which were encountered in this series:

*Case 1:* M. S. (Case number 145392) was a 27-year-old white female housewife. The onset of her ailment dates back to 1936. Diagnosis of cavitory disease on the left side was made in September 1938, and artificial pneumothorax was instituted. This was ineffectual and abandoned within a short period of time. The patient was almost continuously hospitalized for four years prior to her admission to the Metropolitan Hospital in March 1941, with far advanced apparently unilateral pulmonary tuberculosis on the left. There were two large neighboring cavities present within the left lung: one measured 4 by 2 inches in diameter and the other, 1½ by 2 inches in diameter. The larger cavity appeared to be in the left lower lobe, the smaller one in the left upper lobe; both were located posteriorly and mesially (figures 1 and 2). The pericavitary disease was not extensive. The general condition of the patient was fair; however her actual vital capacity was only 1,000 cc., which was 32 per cent of her estimated normal. The patient underwent a Monaldi



FIG. 1. (Upper Left) Case 1: Preoperative chest film of March 6, 1942 reveals far advanced bilateral pulmonary tuberculosis with two large cavities within the left lung.

FIG. 2. (Upper Right) Case 1: Preoperative lateral chest film of March 6, 1942 shows the two giant cavities located posteriorly.

FIG. 3. (Bottom) Case 1: Postoperative chest film of May 13, 1947 shows the bilateral pulmonary tuberculosis controlled and evidence of cavernostomy on the left side.

operation on October 2, 1941, but the tube was removed in six weeks because the cavity remained open and the patient had a hemorrhage from the cavity. On March 9, 1942, the patient underwent a first-stage posterior cavernostomy followed by a second-stage one week later, when the posteriorly located large cavity was unroofed. Through this cavity, the smaller and upper cavity was also opened by removal of the intervening atelectatic lung tissue wall. Since this time, the cavities have been kept open. Smears from the cavities were reported to reveal no acid-fast organisms in September 1942, but tubercle bacilli continued to be discharged in the sputum. At this time further studies (lordotic apical films) revealed a thin walled cavity within the right upper lobe. On complete bed-rest, the cavity did not close. Artificial pneumothorax was instituted on the right side in February 1943, and a selective collapse was obtained leading to the conversion of the sputum in May 1943. The cavernostomy wound became and remained clean and the patient underwent a skin flap operation to the cavity in March 1943, revision of the upper end of the cavernostomy wound, and another skin flap operation in April 1943. The wound was revised again in September and the patient underwent pinch grafting to the cavities during October, November and December, 1943, and in April 1944. After one year of pneumothorax therapy on the right, the space was lost because of obliterative pleuritis. The cavity remained closed on the right side and the sputum continued to be negative for acid-fast bacilli. The operative wound was clean with very little drainage, which did not contain acid-fast organisms. In June 1944, the patient was discharged to her home in excellent condition. Since then she has been followed at the Outpatient Department, where the wound is dressed at weekly intervals. Approximately two-thirds of its surface is covered with epithelium. Several patent bronchial openings are present. There is a minimal mucous drainage present, which is negative for acid-fast or other organisms on smear and on culture. Otherwise the patient is asymptomatic, has gained considerable weight, and attends to her duties as a housewife. In figure 3 may be seen the roentgenogram taken in May 1947, which reveals that the disease is controlled on the right side. In the same film may be seen the cavernostomy on the left side which is now more than five years old.

This case represents a bilateral, far advanced pulmonary tuberculosis, active on both sides. The patient's disease was controlled with artificial pneumothorax on the right side and with cavernostomy on the left side.

*Case 2:* J. M. (Case number 143088) was a 40-year-old white female. The onset of her ailment dates back to 1933. She was admitted to the Metropolitan Hospital for the first time in March 1933, with a right upper lobe cavity disease. Artificial pneumothorax was instituted on the right side in November 1933, and was followed by a phrenic nerve crush (right) in May 1934. Her disease became controlled, her sputum contained no tubercle bacilli and she was discharged to the Outpatient Department in August 1935. She remained well until 1937, when she experienced what was thought to be an attack of rheumatic fever. Her sputum became positive for acid-fast organisms in May 1938. She was readmitted to the Metropolitan Hospital in September 1938 with the pneumothorax still maintained on the right side and cavity disease present on the left. At this time the pneumothorax was abandoned on the right and artificial pneumothorax on the left was attempted unsuccessfully. Attempts to institute artificial pneumothorax were repeated in February and March 1939, and were unsuccessful. The patient's vital capacity was 1,100 which was 37 per cent of her estimated normal. At this time (figure 4) a thin walled cavity, approximately 3 by 3 inches in diameter, was present in the left upper lobe, accompanied by little pericavitary disease.

In June 1940, the patient underwent a Monaldi operation with an anterior approach. This resulted in a closure of the cavity and sputum conversion. However, as soon as the tube was removed, the cavity was reopened and the sputum again became positive for tubercle bacilli.

In June 1942, the patient underwent a one-stage anterior cavernostomy. The sputum became negative for tubercle bacilli within two weeks of the operation. The cavity drainage became negative for tubercle bacilli on smear and culture in September 1942. In November 1942, the patient underwent a revision of the cavernostomy wound, making the drainage tract wider. She underwent skin flap operations to the cavity wall in



FIG. 4. Case 2: Preoperative chest film of April 28, 1942 reveals evidence of fibrothorax on the right side and a large thin walled cavity within the left upper lobe with little pericavitary disease present.

January and March 1943, followed by pinch grafting of the cavity wall in October and December 1943. In March 1944, the patient was discharged to the Outpatient Department with her cavity epithelialized. She has been followed at the clinic and was last seen in May 1947. She is asymptomatic and the wound has remained completely epithelialized. She attends to her duties as a housewife. Chest roentgenograms reveal that the fibrothorax is unchanged on the right and that there is an annular shadow about 3 inches in diameter within the left upper lobe. The latter area represents the drained and epithelialized cavity which clinically appears as a depression of the chest wall lined with skin.

This case represents a bilateral, far advanced pulmonary tuberculosis, active only on the operated side at the time of the cavernostomy. This operative procedure has controlled the disease.

*Case 3:* F. V. (Case number 130-43) was a 33-year-old Puerto Rican female. The onset of her ailment dates back to 1933. Since that time she has been in and out of sanatoriums. In July 1934, artificial pneumothorax was instituted on the right side. Artificial pneumothorax on the left side was started in February 1935 for cavitory disease, and the space was lost because of an obliterative pleuritis. A Jacobaeus operation on the right side was done in August 1940. Subsequently, in October 1940, her sputum became negative for tubercle bacilli, but became positive again in November 1941. In March 1942, there was



FIG. 5. (Left) Case 3: Preoperative chest film of July 8, 1942 shows extensive bilateral cavitory disease with partial pneumothorax on the right side and two distinct cavities within the left lung.

FIG. 6. (Right) Case 3: Postoperative chest film of January 4, 1943 shows massive involvement of both lungs. The right lung is almost completely reexpanded showing multiple cavitation. The left lung shows evidence of the previous cavernostomy.

evidence of reopening of the cavity on the left, which became much larger by June 1942, and tubercle bacilli continued to be present in the sputum.

She was admitted to the Metropolitan Hospital in July 1942 in poor general condition. She was undernourished and underweight at the time of her hospitalization, and expectorated large quantities of purulent material. Chest roentgenograms revealed extensive bilateral cavitory disease with partial pneumothorax on the right and two distinct cavities within the left upper lobe (figure 5). The larger one measured about 3 by 3 inches in diameter and the smaller one about one inch in diameter. There was a considerable amount of infiltrative disease within the pericavitory lung tissue. Her vital capacity was 1,200 cc. which was 46 per cent of the estimated normal.

In March 1942, she underwent a one-stage left lateral cavernostomy. Through the larger cavity the smaller cavity was also opened with the removal of the intervening atelectatic pulmonary wall. The artificial pneumothorax on the right side was maintained, but the disease continued to progress on both sides leading to multiple excavation on the right. The drained cavity on the left continued to discharge large amounts of purulent material. The patient's expectoration decreased, but her dyspnea increased, which necessitated discontinuation of the pneumothorax on the right in December 1943. As may be seen in figure 6, there is a massive involvement of the right lung. The drained cavities on the left were larger than before. The sputum and the wound drainage continued to contain tubercle bacilli and the patient died of progressive respiratory failure on February 10, 1944.

This case represents a bilateral, far advanced pulmonary tuberculosis, active on both sides. Cavernostomy failed to control this hopeless condition.

#### DISCUSSION

Drainage of a tuberculous cavity attacks the focus of the infection itself. The open form of drainage or cavernostomy leaves this part of the lung exposed to direct handling. In this method, the tuberculous cavity heals by sloughing its caseous wall which is removed with the dressing. The pericavitary tissue will be free of the usually high intracavitary pressure and become re-aerated. The cavity wall itself becomes epithelialized from the patent bronchial openings or from the skin edges. The latter is usually helped by grafting skin to the cavity surface, as was done successfully in 3 of the 5 discharged patients. Apparently the diversion of the flow of the tuberculous pus from the other areas of the lung frequently leads to controlling or arresting the disease in those areas as well. Extracavitary foci of tuberculosis may take their own course of healing if they are not continuously showered with tuberculous secretion. The less the pericavitary disease, the more hopeful is the case. If multiple cavities are present, they can be united if they are located near to each other and the intervening lung tissue wall is atelectatic or can be made so. There were two such operations in the present series. In both cases, one connecting cavity was made out of two neighboring ones by the removal of the intervening wall. One of these patients is well (M. S.); the other one died (F. V.). The patient who did well had very little pericavitary disease; the one who died had extensive pericavitary involvement. Almost all of our cases were on the verge of becoming respiratory cripples and their vital capacities were too low to permit any extensive surgical procedure.

One of the values of cavernostomy is that it is a selective procedure. Very little functioning lung tissue need be sacrificed when this operation is performed and consequently it can be safely applied even on cases with a borderline respiratory capacity. In only one case out of the 22, did thoracoplasty precede the cavernostomy. In the other 21 cases, cavernostomy was applied as a procedure independent of thoracoplasty. This is contrary to the application of the procedure by Eloesser and his coworkers (4), who used cavernostomy for post-thoracoplasty tension cavities. It is obvious from this series that the cases with controlled disease on the contralateral side did far better than the ones with

active disease on both sides. Most of these patients had many other procedures applied prior to their cavernostomy. All of these patients belonged in a group for whom no hope of cure could be offered. A procedure which saved 12 (51.5 per cent) of the patients from a group of the type here described is worthy of recommendation.

The indications for cavernostomy on these patients were as follows: (1) Bilateral, far advanced disease with controlled contralateral side and one or more large cavities present on the active side, with little or no pericavitary disease present; (2) unilateral cases presenting the same type of disease on the active side as noted above, on whom more extensive surgery was contraindicated because of a low respiratory capacity; (3) cases with a residual cavity under a thoracoplasty where revision of the thoracoplasty or excisional surgery was contraindicated; (4) bilateral, far advanced cases with the disease active on both sides and one or more cavities present on the operative side.

#### SUMMARY

During a five year period cavernostomies were performed at the Metropolitan Hospital in 22 tuberculous patients whose prognosis was considered to be hopeless. Twelve of these patients are alive and 5 are well. Another 5 patients are only clinically improved and 2 most likely will not get well. Even in this group of 2, however, life has been extended and symptoms have cleared to a great extent.

The indications for cavernostomy in this series of 22 patients are enumerated.

#### SUMARIO

##### *Cavernostomía*

Durante un quinquenio ejecutáronse cavernostomías en el hospital donde trabaja el A. en 22 tuberculosos desahuciados. Doce de esos enfermos están vivos todavía y cinco se hallan bien, otros cinco sólo clínicamente mejorados y dos con toda probabilidad no se repondrán. Sin embargo, aun en este grupo de siete, se ha alargado la vida y los síntomas han desaparecido en gran parte.

Enuméranse las indicaciones de la cavernostomía en esta serie de 22 enfermos.

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## THE SIGNIFICANCE OF PULMONARY TUBERCULOSIS WHEN ASSOCIATED WITH BRONCHOGENIC CARCINOMA<sup>1</sup>

GEORGE W. DRYMAJSKI AND HENRY C. SWEANY

In 2,000 consecutive autopsies performed at the Municipal Tuberculosis Sanitarium from 1917 to 1946 there were 57 cases of bronchogenic carcinoma, 15 (26 per cent) of which had discharged acid-fast bacilli in the sputum. The purpose of this report is not to review the literature concerning the association of tuberculosis with carcinoma but, rather, to evaluate the clinical significance of acid-fast bacilli in the sputum of patients with bronchogenic carcinoma.

The question of an antagonism between tuberculosis and carcinoma, postulated almost a century ago by Rokitsansky (1), is little nearer solution now so far as statistical evidence or experimental proof is concerned. The earlier statistics did not take into consideration the fact that the two diseases affect the opposite extremes of life, and for that reason direct comparisons were inaccurate. Other comparisons were also faulty. For example, cancer is prone to develop in the more vigorous type of cells found in the robust individual who is relatively immune to infectious or debilitating diseases. Tuberculosis, on the other hand, seems more prone to develop in the low-resistance or nonreacting individual in whom cancer is less likely to develop. It would be risky, from the evidence at hand, to claim that an antagonism exists between tuberculosis and carcinoma. It is, however, rather evident that neither disease predisposes to the other and yet the two diseases are not infrequently associated. Because of this occasional coexistence the problem of therapy becomes complicated.

### COMMENT

In table 1 may be seen a summary of the case reports of the 15 patients with bronchogenic carcinoma who had discharged acid-fast bacilli during life. Of the 15 cases, 5 (cases 4, 5, 6, 7, and 8) had far advanced active tuberculosis which terminated in caseous pneumonia in four instances. In one patient (case 8), the carcinoma measured only a few centimeters and was considered an incidental finding. Chronic fibroid tuberculosis was evident in cases 4 and 7, and, as determined from the history, had been active for years. Cases 5 and 7 had no previous pulmonary symptoms. The sputum of the 5 patients with far advanced tuberculosis was repeatedly positive for tubercle bacilli.

Three cases (Cases 1, 2, and 3) showed evidence of secondary pulmonary tuberculosis. Fibrocaseous in character, these lesions were well encapsulated and without perifocal inflammatory changes of exudation, congestion, or cellular infiltration. One patient (case 1) had been treated for far advanced tuberculosis for several years. His sputum had become negative for tubercle bacilli and he was an apparently arrested case of far advanced pulmonary tuberculosis when a bronchogenic squamous cell carcinoma caused his death. At autopsy there

<sup>1</sup> From the Research Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium.



was no exacerbation of the healing, encapsulated tuberculous lesions. It is curious that the anthracosilico tuberculosis of case 2 was not reactivated, although tumor cells had invaded an old caseous focus. In another patient (case 3), who had suffered no previous pulmonary symptoms, the tuberculosis was moderately

TABLE I  
*Summary of case reports*

| CASE NUMBER | AGE | NUMBER OF SPUTUM SPECIMENS POSITIVE FOR ACID-FAST BACILLI | LOCATION OF TUBERCULOSIS              | TYPE OF TUBERCULOSIS         | LOCATION OF CARCINOMA | TYPE OF CARCINOMA |
|-------------|-----|---|---------------------------------------|------------------------------|-----------------------|-------------------|
| 1           | 63  | Repeatedly positive                                       | Right upper lobe                      | Fibrotic                     | Right main bronchus   | Squamous cell     |
| 2           | 47  | Two   | Right apex                            | Fibrotic silico-tuberculosis | Left lung             | Squamous cell     |
| 3           | 63  | Tubercle bacilli cultured on one occasion                 | Right apex                            | Fibrotic                     | Both lungs            | Adeno-carcinoma   |
| 4           | 50  | Repeatedly positive                                       | Bilateral                             | Pneumonic                    | Left lower lobe       | Squamous cell     |
| 5           | 42  | Persistently positive                                     | Right upper lobe                      | Ulcerative                   | Left main bronchus    | Squamous cell     |
| 6           | 39  | Repeatedly positive                                       | Right upper lobe                      | Pneumonic                    | Right main bronchus   | Oat cell          |
| 7           | 67  | Several   | Right lung                            | Pneumonic                    | Right lung            | Squamous cell     |
| 8           | 60  | Repeatedly positive                                       | Both lungs                            | Ulcerative                   | Right apex            | Squamous cell     |
| 9           | 42  | One   | Bronchial lymph node                  | Calcified                    | Left apex             | Oat cell          |
| 10          | 44  | One   | Both lungs and bronchial lymph nodes  | Calcified and fibrotic       | Both lungs            | Adenomatous       |
| 11          | 70  | Two   | Both lungs                            | Fibrotic and calcified       | Left main bronchus    | Adeno-carcinoma   |
| 12          | 56  | Two   | —                                     | —                            | Left upper lobe       | Basal cell        |
| 13          | 43  | Two   | Right upper lobe and right hilar node | Calcified                    | Left main bronchus    | Squamous cell     |
| 14          | 48  | One   | —                                     | —                            | Right lung            | Squamous cell     |
| 15          | 60  | One   | —                                     | —                            | Right lower lobe      | Adeno-carcinoma   |

advanced and inactive. The sputum obtained from these 3 patients during life was occasionally positive for tubercle bacilli.

Other than the equivocal evidence of calcified nodules in the pulmonary lymph nodes or in the lung parenchyma, 5 cases (Cases 9, 10, 11, 12, and 13) showed no signs of tuberculosis. In 2 cases (Cases 14 and 15), not even calcified nodules were found. The sputum of these latter 7 cases had contained acid-fast organisms on one or two occasions. There was no instance of carcinoma developing from the metaplastic epithelium lining an old tuberculous ulceration.

Fried (2), in reporting 13 cases of bronchogenic carcinoma associated with pulmonary tuberculosis, observed that the tuberculous lesions were fibroid in all cases. The sputum positive for tubercle bacilli in 3 of his cases.

The inability to discover at necropsy tuberculous pulmonary lesions furnishes no explanation for the finding of acid-fast bacilli in the sputum of 7 cases of bronchogenic carcinoma. However, from 10 to 20 per cent of adult patients who die of causes other than tuberculosis have living tubercle bacilli in their lungs (3), and approximately 5 to 10 per cent of the population of the United States harbor living tubercle bacilli (4). It is not beyond the realm of the possible, then, to assume that the malignant process in these instances had literally liquidated and finally destroyed a tuberculous focus, which, containing bacilli, merely happened to be in the path of the irresistible neoplasm. Sputum examined during this critical period would contain acid-fast organisms which had originated from a short-lived reactivation of the tuberculous lesion.

The Municipal Tuberculosis Sanitarium also serves as a clearing house for all patients who have suspicious pulmonary lesions or a sputum which contains acid-fast organisms. The high incidence (26 per cent) of cases of bronchogenic carcinoma with tubercle bacilli in the sputum must be interpreted accordingly.

#### SUMMARY

1. In 2,000 autopsies at the Municipal Tuberculosis Sanitarium of Chicago, there were 57 (2.8 per cent) cases of bronchogenic carcinoma. Fifteen (26 per cent) of these patients had discharged acid-fast bacilli in the sputum during life.

2. Of these 15 cases of bronchogenic carcinoma associated with acid-fast organisms in the sputum, there were 5 cases of florid, far advanced pulmonary tuberculosis, 3 cases of arrested secondary tuberculosis, and 7 cases in which definite tuberculous lesions were not found.

3. The presence of tubercle bacilli in the sputum does not necessarily exclude the presence of an underlying bronchogenic carcinoma. Neither does the presence of carcinoma exclude tuberculosis. The search for each disease should be carried out regardless of any positive findings of the other.

4. If the sputum contains tubercle bacilli in cases of bronchogenic carcinoma, the extent or nature of the pulmonary tuberculosis need not necessarily prohibit active surgical measures. In two-thirds of the cases, the presence of acid-fast organisms in the sputum must be considered of secondary or minor importance.

#### SUMARIO

##### *Significación de la Tuberculosis Pulmonar Asociada a Carcinoma Broncogénico*

1. Entre 2,000 autopsias ejecutadas en el Sanitario Municipal para Tuberculosis de Chicago, hubo 57 (2.8 por ciento) casos de carcinoma broncogénico, 15 (26 por ciento) de los cuales estaban asociados con un esputo positivo para bacilos tuberculosos.

2. De esos 15 casos de carcinoma broncogénico asociado con gérmenes ácido-resistentes en el esputo, en 5 había tuberculosis pulmonar florida, muy avanzada

y en 3 tuberculosis secundaria estacionada, en tanto que en 7 no se observaron lesiones tuberculosas bien definidas.

3. La presencia de bacilos tuberculosos en el esputo no excluye forzosamente la presencia de un carcinoma broncogénico subyacente. Tampoco excluye la presencia de carcinoma una tuberculosis. La busca de cada enfermedad debe llevarse a cabo independientemente de los hallazgos relativos a la otra.

4. Si, en casos de carcinoma broncogénico, el esputo contiene bacilos tuberculosos, la extensión o naturaleza de la tuberculosis pulmonar no veda forzosamente el empleo de providencias quirúrgicas activas. En dos terceras partes de los casos, debe considerarse como de importancia secundaria o menor la presencia de microbios ácidosresistentes en el esputo.

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# BRONCHIAL TUBERCULOSIS SIMULATING FOREIGN BODY IN A CHILD ONE YEAR OF AGE

Report of a Case

PORTER P. VINSON<sup>1</sup>

Tuberculosis may simulate any type of pulmonary disease, and when a bronchus is partly or completely occluded by an intrabronchial mass of tuberculous granulation tissue, or by a tuberculous node pressing on a bronchus with compression and reduction of the bronchial lumen, the presence of a foreign body may be suspected.

Differentiation of foreign body from bronchial tuberculosis may be difficult in adults, especially when a healed, calcified, tuberculous lymph node, a so-called lung stone, erodes through the bronchial wall and actually exists as an intrabronchial foreign body. In infancy and childhood calcified hilar lymph nodes seldom, if ever, enter the lumen of a bronchus, but nodes enlarged by tuberculous infection may reduce the bronchial lumen and produce physical signs, clinical symptoms, and roentgenoscopic evidence suggestive of the presence of an intrabronchial foreign body.

The following case is reported because of many unusual findings and a history that suggested aspiration of a foreign body.

## CASE REPORT

A child, one year of age, was brought for examination November 14, 1947. Several weeks previously, the mother had noticed that the child had been chewing on a shoe lace and she was afraid that the tip on the lace might be swallowed. A few days later, five weeks before the child was examined on this service, the mother had found that the tip on the shoe lace had disappeared. Although the patient had not had any symptoms that indicated ingestion or inhalation of a foreign body, the mother concluded that the tip had been swallowed. Two weeks later, the child began to have cough and wheezing that increased in severity and became associated with intermittent attacks of dyspnea. For forty-eight hours prior to examination by the writer, dyspnea had been sufficiently severe to require administration of oxygen.

Roentgenoscopic examination revealed depression of the diaphragm on the right side, with emphysema of the entire right lung and shifting of the heart and mediastinal structures toward the left side (figure 1). Fluoroscopic study showed almost complete immobility of the diaphragm on the right in the position of extreme inspiration. Physical examination of the thorax disclosed evidence of marked obstructive emphysema of the right lung.

The child's father, who was forty-three years of age, was employed as a sheet metal worker and considered himself in good health, although he had been discharged from the Army in 1936 with a diagnosis of "arrested pulmonary tuberculosis." In view of the family history of tuberculosis with the probability of direct exposure, and the fact that the child had not had any respiratory symptoms until two weeks after the tip had dis-

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appeared from the shoe lace, tuberculous disease obstructing the bronchus was considered a more likely cause of symptoms than foreign body.

Bronchoscopic examination was performed on November 15, 1947, and the right main bronchus was found to be almost completely occluded by a mass of granulomatous tissue that bled freely on manipulation. A foreign body could not be identified. Tissue was



FIG. 1. Roentgenogram showing depression of diaphragm on right, emphysema of entire right lung, and shifting of heart and mediastinal structures toward left.

removed for microscopic study, and smears were made for examination for tubercle bacilli. Significant organisms could not be found, and study of the tissue revealed marked necrosis only. The child, however, showed a strongly positive reaction to a cutaneous injection of Old Tuberculin in a dilution of 1:100,000 and many acid-fast organisms were demonstrated in the stained sections of the tissue.

The father was then examined and was found to have bilateral pulmonary tuberculosis with multiple small cavities in the upper lobe of the left lung. Examination of his sputum disclosed the presence of tubercle bacilli.

The child was treated for ten days by administration of streptomycin and deep roentgenotherapy. At the time of dismissal the breath sounds were equal on both sides and

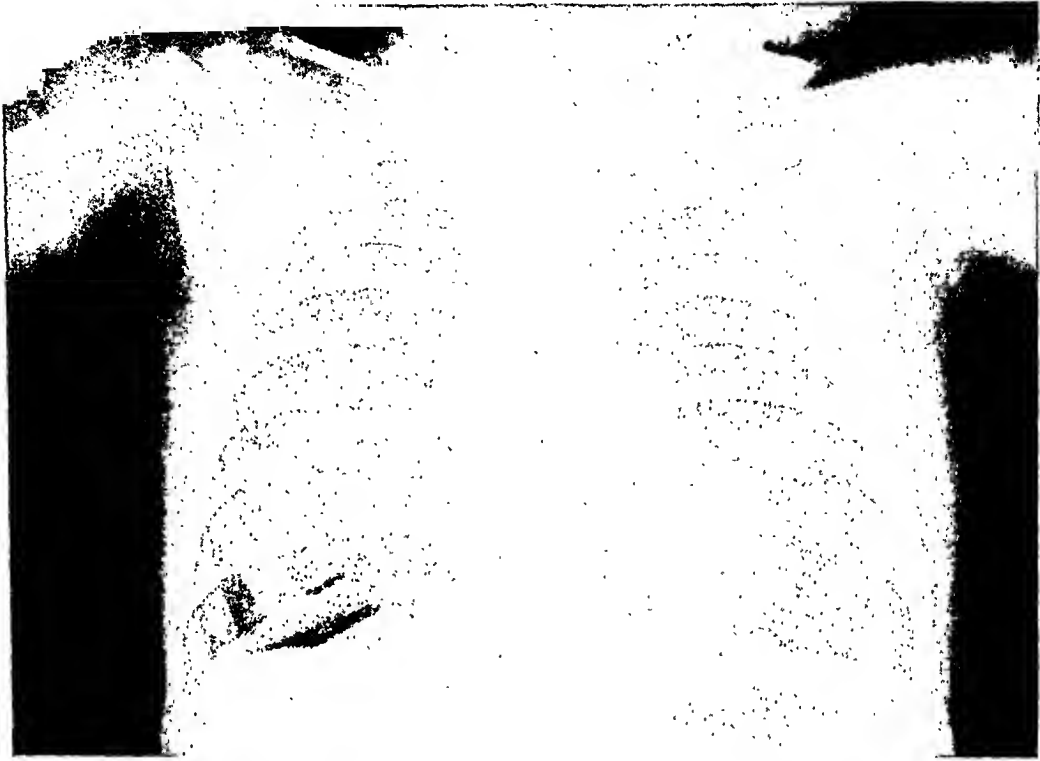


FIG. 2. Roentgenogram after treatment, showing normal aeration on both sides, with slight infiltration in right hilar area.

cough and stridor had disappeared. Roentgenoscopic examination showed normal aeration on both sides, with slight evidence of infiltration in the right hilar area (figure 2).

Facilities at home were unsatisfactory for continuation of streptomycin therapy, and administration of the drug was, therefore, discontinued. The child was dismissed on November 24, 1947.

# THE EFFECT OF SALICYLIC ACID ON THE GROWTH, MORPHOLOGY AND VIRULENCE OF *M. TUBERCULOSIS*<sup>1,2</sup>

ROBERT J. FITZGERALD AND FREDERICK BERNHEIM

Salicylic acid added to suspensions of virulent tubercle bacilli of both the H37 and B<sub>1</sub> strains increases the oxygen uptake of the bacteria (1). This effect, which is catalytic because the salicylic acid is not metabolized, is absent or much less marked in avirulent tubercle bacilli and other mycobacteria (2, 3). Attempts to elucidate the mechanism of the salicylic acid effect by the Warburg technique have thus far failed. It was possible that information on this effect could be obtained if the bacteria were adapted to grow in salicylic acid. This was accordingly done and the results are described in the following.

## EXPERIMENTAL

The H37RV strain of *Mycobacterium tuberculosis* was obtained from the Trudeau collection and grown in veal infusion glycerin broth. The growth of this strain is partially inhibited by 5.0 mg. per cent of salicylic acid. By successive transfers into increasing concentrations, it has been finally possible to obtain growth at 50 mg. per cent of the drug. Similar adaptation was also obtained with benzoic acid, which also acts catalytically on the oxygen uptake of virulent strains. The growth rate at these high concentrations is about 50 per cent slower than normal.

In the presence of 10 mg. per cent or more of salicylic acid, the gross characteristics of the culture change. Instead of the normal yellowish-white thick mat which is easily friable, the growth is thin, membranous, rubbery and of darker color. When the cultures were twenty days old, smears were made and stained simultaneously by the Ziehl-Neelsen technique. Photomicrographs of these smears may be seen in figure 1. The cells grown in salicylic acid are much longer and wider than the normal, and have relatively few granules. In contrast, the cells grown in benzoic acid are very little different from normal, both in the gross aspect of the culture and in the microscopic characteristics of the individual cells.

After one subculture in normal medium cells altered by their growth in salicylic acid revert to normal as regards their morphological and physiological characteristics.

The virulence of an H37RV strain which had been grown for three generations in the presence of 25 mg. per cent salicylic acid was tested by the guinea pig omentum method of Saz et al. (4). The inoculum contained 0.001 mg. moist weight of the organism, in order that any differences in virulence might be more apparent. The control pigs received the same quantity of the normal parent H37RV strain. The animals were sacrificed after fourteen days and the omen-

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<sup>2</sup> Aided by a grant from the Duke University Research Council.



FIG. 1. Left: Normal cells. Right: cells grown in 25 mg. per cent salicylic acid,  $\times 1600$  approximately.



tum removed and weighed. The results, presented in table 1, indicate a definite increase in virulence of the salicylate cells for the guinea pig as assayed by this method. A second test using organisms from the fourth subculture in medium

TABLE 1

*A comparison of the virulence of normal and salicylate adapted strains of M. tuberculosis as determined by the guinea pig omentum test*

| PIG NUMBER | NORMAL H37RV (0.001 mg.) |         |      | H37RV—SAL.* (0.001 mg.) |         |      |
|------------|--------------------------|---------|------|-------------------------|---------|------|
|            | Weight                   | Omentum | R**  | Weight                  | Omentum | R**  |
| 1          | 462                      | 2.3     | 0.50 | 405                     | 4.2     | 1.03 |
| 2          | 470                      | 3.1     | 0.66 | 480                     | 4.1     | 0.85 |
| 3          | 474                      | 3.0     | 0.63 | 486                     | 3.9     | 0.80 |
| 4          | 500                      | 3.0     | 0.60 | 490                     | 4.0     | 0.82 |
| 5          | 510                      | 3.2     | 0.59 | 526                     | 4.2     | 0.80 |
| 6          | 550                      | 3.0     | 0.55 |                         |         |      |
| Average.   | 490                      | 2.9     | 0.59 | 477                     | 4.1     | 0.87 |

\* *M. tuberculosis* H37RV third generation grown in the presence of 25 mg. per cent salicylic acid.

\*\* R = Omentum wt. per 100 gm. guinea pig weight.

TABLE 2

*The effect of various compounds on the oxygen uptake of benzoic and salicylate adapted strains of M. tuberculosis H37RV<sup>1</sup>*

| TIME | NORMAL STRAIN    |                    |                          | BENZOATE STRAIN <sup>2</sup> |                    |                          | SALICYLATE STRAIN <sup>3</sup> |                    |                          |
|------|------------------|--------------------|--------------------------|------------------------------|--------------------|--------------------------|--------------------------------|--------------------|--------------------------|
|      | 1.0 mg. Benzoate | 1.0 mg. Salicylate | 1.0 mg. PAS <sup>4</sup> | 1.0 mg. Benzoate             | 1.0 mg. Salicylate | 1.0 mg. PAS <sup>4</sup> | 1.0 mg. Benzoate               | 1.0 mg. Salicylate | 1.0 mg. PAS <sup>4</sup> |
| hr.  | mm.              | mm.                | mm.                      | mm.                          | mm.                | mm.                      | mm.                            | mm.                | mm.                      |
| 0:50 | 22               | 19                 | 7                        | 10                           | 17                 | -4                       | -2                             | -5                 | -5                       |
| 1:35 | 48               | 28                 | 11                       | 15                           | 22                 | -6                       | 0                              | -8                 | -7                       |
| 2:35 | 89               | 46                 | 14                       | 17                           | 27                 | -6                       | 1                              | -15                | -11                      |
| 3:50 | 138              | 65                 | 17                       | 25                           | 32                 | -3                       | 3                              | -23                | -9                       |
| 4:50 | 172              | 85                 | 21                       | 25                           | 36                 | -1                       | 3                              | -29                | -11                      |
| 5:35 | 202              | 103                | 26                       | 27                           | 36                 | -3                       | 1                              | -34                | -13                      |

<sup>1</sup> The oxygen uptake of the controls without added substrate has been subtracted in each case. pH 6.7, 37°C.

<sup>2</sup> Grown for 3 generations in the presence of 39 mg. per cent benzoate.

<sup>3</sup> Grown for 3 generations in the presence of 25 mg. per cent salicylate.

<sup>4</sup> p amino salicylic acid

containing 25 mg. per cent salicylic acid gave similar results. Whether this apparent increase in virulence is transient or will persist remains to be investigated.

In virulent strains previously studied, salicylic acid produced a greater acceleration of oxygen uptake than benzoic acid (1). As may be seen in table 2, benzoic acid produces the larger effect with the present strain. Acceleration to

markedly depressed in cells grown with either of the two compounds. This indicates that the metabolites present in normal cells, the oxidation of which can be catalyzed by salicylic or benzoic acids, have not accumulated in the cells grown in their presence. Para-aminosalicylic acid, developed by Lehmann (3) on the basis of the salicylic acid effect as a possible chemotherapeutic agent for tuberculosis, accelerates the oxygen uptake of normal cells to a small extent, but is without effect on the uptake of cells grown in benzoic or salicylic acids.

The bacteriostatic action of p-aminosalicylic acid on virulent tubercle bacilli is not antagonized by small concentrations of either benzoic or salicylic acids. It was of interest, however, to test its effect on the cells grown with salicylic

TABLE 3

*The Effect of p-amino salicylic acid (P.A.S.) on the growth of the normal and salicylate strains of H37RV*

| P.A.S. CONCENTRATION<br>Mg. Per cent | NORMAL H37RV  |                     | SALICYLATE ADAPTED H37RV |                     |
|--------------------------------------|---------------|---------------------|--------------------------|---------------------|
|                                      | Growth* (gm.) | Per cent inhibition | Growth (gm.)             | Per cent inhibition |
| 5.0                                  | 0.025         | 94                  | 0.045                    | 85                  |
| 1.0                                  | 0.085         | 78                  | 0.125                    | 55                  |
| 0.5                                  | 0.09          | 77                  | 0.13                     | 57                  |
| 0.0                                  | 0.39          | —                   | 0.29                     | —                   |

\* The cultures were fourteen days old at the time the determinations were made. The per cent inhibition was calculated from the following formula

$$100 - \left( \frac{\text{wt. of growth at "x" mg. per cent P.A.S.}}{\text{wt. of growth at 0.0 mg. per cent P.A.S.}} \times 100 \right) \text{ for each strain.}$$

acid. In table 3, it may be seen that this latter strain is more resistant to the inhibition by p-aminosalicylic acid than the normal parent strain.

#### DISCUSSION

These experiments do not elucidate the exact mechanism of action of salicylic acid. They do, however, show that the metabolic effect observed in the Warburg vessel on nonproliferating cells is of such a nature that the morphological characteristics, the virulence, and the reaction to a drug of cells grown with salicylic acid are profoundly altered. It should be noted that these changes are less marked in cells grown in benzoic acid, despite the fact that a greater acceleration of oxygen uptake occurs in the Warburg vessel. Therefore the specific configuration of salicylic acid is apparently of great importance in causing the changes observed.

#### SUMMARY

Organisms of the H37RV strain of *Mycobacterium tuberculosis*, adapted to grow in high concentrations of salicylic acid, show an increased size, an apparent increase in virulence, and metabolic reactions which differ from the normal.

## SUMARIO

*Efecto del Acido Salicílico sobre el Crecimiento, Morfología y Virulencia del Bacilo Tuberculoso*

Microbios de la cepa H37RV del *Mycobacterium tuberculosis*, una vez adaptados al crecimiento en altas concentraciones de ácido salicílico, revelan aumento en su tamaño y virulencia y reacciones metabólicas que se apartan de lo normal.

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# SUBMERGED SUSPENDED LIQUID CULTURE OF *M. TUBERCULOSIS* AND OTHER ACID-FAST BACILLI UNDER THE INFLUENCE OF PHYSICAL AND CHEMICAL FACTORS<sup>1,2</sup>

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## INTRODUCTION

The cultivation or growth of acid-fast bacilli, including tubercle bacilli, has interested scientific investigators since the discovery of the tubercle bacillus by Robert Koch in 1882. Although marked strides have been made, many of the obvious facts concerning the growth of tubercle bacilli were noted by early students, Koch particularly, and his contemporaries and colleagues. Koch described the main characteristics of the tubercle bacillus: slow in growth, "acid-fast" characteristics, resistant to reagents, able to grow on relatively simple nutrients, tending to grow in lumps but, above all, an aerobe which preferred to grow on the surface of liquid media. Therefore, Koch chose solid media except when preparing biological products such as tuberculin. He observed all this, despite his lack of fine quantitative conceptions, the modern concept of nutrients, and the essential action of hormones and vitamins. He also illustrated and described the developing skein form of growth cultures when examined at low and high magnification.

The significance of nutrients was stressed further in the tuberculin studies of Long (1). Their importance for cultural diagnostic purposes (2) was also emphasized when it was found that simple synthetic media were unsuited to this purpose but that tubercle bacilli required the more complex natural nutrients when planted in small numbers. Thus developed the practical diagnostic media to replace animal tests; media in which the potato, blood and tissues, and egg products, the yolk in particular (3), were utilized. The success with the coagulated yolk in 1932 led to the suggestion for its use, as well as the use of blood, in a simple practical technique for diagnostic purposes, in which the microscopic examination for positive acid-fast bacilli in skein formation (seen even in low power magnification) obviated the need for a previously laboratory-prepared sterile medium (4). This procedure, although sound bacteriologically, never became acceptable practically because the method required the use of the stained smear and because it could only disclose acid-fast bacilli. Such was not the case when solid media were used which disclosed the characteristics of the gross colony so essential to the biologic concept of tubercle bacilli. The criterion of using the acid-fast skein as evidence of growth apparently could not overcome these objections.

About this same time, Kirschner (5, 6) published his observations with depth, or submerged, culture of the tubercle bacillus on suitable liquid nutrients. In these experiments, he tried essentially three liquid media: (1) a synthetic nu-

<sup>1</sup> From the Research Department, National Jewish Hospital, Denver, Colorado.

<sup>2</sup> This investigation was aided by a gift from Morton May, in memory of Florence G. May.

trient with 10 per cent serum (designated "Sy-Ser"), (2) a mineral salt solution with 10 per cent serum ("Min-Ser"), and (3) a mineral salt-asparagin solution with 10 per cent serum ("Minas-Ser"). With these media, macroscopic growth appeared in six to ten days after heavy planting, while sparse plants required two to three weeks for discernible colonies to develop. Growth occurred as a number of fine gray white lumps, which attained the size of the head of a pin and, when sufficiently numerous, resulted in a millimeter thick membrane covering the bottom of the tube. The liquid remained clear. The sediment, however, was never homogeneous nor did it form a turbid liquid. This latter criterion was used by Kirschner to differentiate growth of tubercle bacilli from contamination. For diagnostic purposes, these liquid media were compared by Kirschner with solid nutrients (Hohn, Loewenstein, Petroff, and Petragnani, egg media). As a result of Kirschner's observations, it is concluded from the study of human tubercle bacilli that the egg media are superior to the liquid submerged culture, especially with turbid preparations producing a sediment in the liquid. The liquid media also require microscopic control in doubtful tests which is obviated in solid egg media. In spite of contamination (especially with sarcinae or diphtheria-like organisms), at times the liquid media yielded typical tubercle bacillus cultures, while egg (solid medium) cultures were valueless because of the contaminant. Depth culture should not replace egg media for diagnostic purposes, according to Kirschner in one of his reports, but should be used in conjunction with them, especially when dealing with uncontaminated, non-purulent exudates, for 1.0 to 3.0 cc. of such material can be planted directly into the liquid medium. Moreover, he believes that the deep culture is better suited to studying the effect of certain dissolved substances on tubercle bacilli.

In a study with bovine tubercle bacilli, Kirschner notes that growth in "Sy-Ser" is rapid for human and bovine laboratory strains with secondary surface growth. He notes here also that for diagnostic culture of human source material, this medium is equal to the egg media and growth appears earlier; while with bovine bacilli, the "Minas-Ser" cultures exceeded the cultures on egg media. Human tubercle bacilli grow well on egg media and equally well in the liquid media. The growth of bovine bacilli on egg media is slow and sparse, in the "Sy-Ser" tubes there is usually no growth, while in the "Minas-Ser" tubes a good sediment growth occurs. Kirschner suggests this difference may be used as a differential test.

Interest in subsurface growth of tubercle bacilli waned until Drea (7) and Cohn (8) again demonstrated its existence under certain conditions, but not to the extent of surface growth. In 1944, Youmans (9) grew virulent human tubercle bacilli in a synthetic medium and claimed evident growth in two days, which rapidly increased and consisted of the growth of tubercle bacilli between the medium and the side of the tube when 10 cc. of medium in a 200 by 25 mm. tube was used. No dispersing agent was used in making suspensions of the tubercle bacilli. The larger inocula grew more rapidly (0.01 to 0.001 mg. required two to four weeks for subsurface growth), and finer suspensions seemed to grow more rapidly. The same subsurface growth was observed in 250 cc.

flasks containing 100 cc. of medium. No mention was made of the importance of the depth of liquid. This method of subsurface growth was used by Youmans for testing sulfone (10) drugs and streptomycin (11).

In 1945, Dubos (12) noted that rapid submerged growth "throughout the fluid" can be obtained in lipid media. Saprophytic and avian strains grow within one day, and bovine and human strains within three days. The addition of purified serum albumin (0.1 per cent or less) to these liquid media further enhances the growth of tubercle bacilli and permits in particular more rapid multiplication of small inocula. Certain water-soluble esters of long chain fatty acids (in particular, oleic acid) favor submerged and diffuse growth of mycobacteria throughout the depth of synthetic liquid media (13). In 1946 (14), a Tween-albumin liquid medium was described along the same lines for the purpose of isolating tubercle bacilli from pathological materials from tuberculous patients with positive results in materials negative on microscopic examination of concentrated material. The fact that these media permit the production of young and homogeneous cultures suggests that they may facilitate the study of some of the problems of tuberculosis. Foley (15) found several variations of Dubos' media invaluable in the laboratory diagnosis of tuberculosis, but noted they would support the growth of a variety of nonacid-fast microorganisms as well as acid-fast saprophytes. He states that "they cannot be used alone for the specific bacteriologic identification of tubercle bacilli." He suggests accordingly a combination of rapid liquid culture with guinea pig confirmation. A comparison of the essential constituents and amounts in the various liquid media (Kirschner's, Dubos', Youmans', Long's and Wong's) is enlightening as to the slight differences between them from a cultural viewpoint.

Fundamentally all the liquid media noted in table 1 contain about the same essential salt constituents. Kirschner's medium (1932) and Dubos' medium (1946) are practically the same composition except for the addition of "Tween 80" in the latter. Kirschner described the essentials for subsurface culture in salt media, and to this Youmans and Dubos have added little further information. The objection to Kirschner's studies was that they were not performed on a quantitative basis so far as the bacilli were concerned, but otherwise the essential findings were noted by him. The function of serum or plasma in the medium was not described satisfactorily in either case thus far, although the shallow liquid is adhered to, again without apparent satisfactory explanation. The significance of the oxygen (or air) problem has been referred to previously by Corper (16), Novy (17), Rich and Follis (18), and Cohn (8).

*The growth of tubercle bacilli in liquid cultures:* There appears to be some disparity in opinion concerning the growth of tubercle bacilli on the surface and submerged in liquid media, as compared with their growth on solid media of good nutrient qualities. It is well known from past experience that the addition of agar adds no material benefit to the nutrient qualities of a medium for acid-fast or tubercle bacilli and may even be detrimental in that the contained nutrient becomes less available as indicated by the larger plantings required to obtain positive cultures on such media. However, when requiring certain types of

culture, this loss in efficiency can be compensated for by the greater amount of plants used for initiating growth. In the case of liquid media, there are two types of recognized positive culture growth, and usually the surface cultures have been given greater consideration in the past. Large volumes of liquid were used, the depth precluded a consideration of submerged growth, and the yield of bacillary mass was important and a primary item in the use of such media.

Since submerged cultures have attracted interest recently, a practical and comparative evaluation seemed pertinent at this time, especially in view of Kirschner's earlier observations. It was obvious that the gross appearance could not designate acid-fast or tubercle bacilli without recourse to the micro-

TABLE 1  
*Essential salt composition of liquid media used for submerged culture  
compared with Long's and Wong's nonprotein synthetic medium*

| REAGENT  | LONG*—<br>1926 | WONG*—<br>1936 | KIRSCHNER**—<br>1932   | YOUNG**<br>—1944 | DUBOS**—<br>1946 |
|--|----------------|----------------|------------------------|------------------|------------------|
|  |                |                |                        | NaOH—<br>Neutral |                  |
| Disodium phosphate ( $\text{Na}_2\text{HPO}_4$ ).....  | 0              | 0              | 3                      | 0                | 6.3              |
| Monopotassium phosphate ( $\text{KH}_2\text{PO}_4$ ).. | 3              | 6              | 4                      | 5                | 1.0              |
| Magnesium sulphate ( $\text{MgSO}_4$ ).....            | 1              | 1              | 0.6                    | 0.5              | 0.6              |
| Sodium citrate.....                                    | 0              | 0              | 2.5                    | 2.5              | 1.5              |
| Ammonium citrate.....                                  | 5              | 5              | 0                      | 0                | 0                |
| Sodium carbonate.....                                  | 3              | 2              | 0                      | 0                | 0                |
| Asparagin.....   | 5              | 0              | 0.5-5                  | 5                | 1.0              |
| Malate (as acid).....                                  | 0              | 3              | 0                      | 0                | 0                |
| Glycerol.....  | 50             | 50             | 20 with and<br>without | 20               | Claimed<br>toxic |
| Ferric ammonium citrate.....                           | 0.05           | 0.05           | 0                      | 0                | 0.1              |
| Sodium chloride.....                                   | 1              | 2              | 0                      | 0                | 0                |
| Tween 80.....  | 0              | 0              | 0                      | 0                | 0.5              |

All add distilled water to make 1,000 cc. of liquid.

\* Long: Am. Rev. Tuberc., 1926, 13, 393. Wong: Am. Rev. Tuberc., 1936, 33, 577.

\*\* Kirschner adds 10 per cent serum to some of his media; Youmans adds 10 per cent plasma; Dubos adds bovine V fraction of albumin in his later media.

scopic stained smear preparation for verification, and even then the problem of acid-fast saprophytes, as distinguished from tubercle bacilli, remained unsolved by such procedure. Gross characteristics do not suffice to differentiate, as in the case of solid medium cultures where definite characteristic specific colonies can be recognized. The criteria to be used for submerged growth also enter, particularly in suspected or planted specimens where sedimentation and concentration may lead to erroneous deductions with liquid cultures. A study of the liquid cultures planted with graded amounts of fine suspensions of human tubercle bacilli on various modifications of well-known liquids is recorded in table 2.

## EXPERIMENTAL OBSERVATIONS

The results recorded in table 2 indicate that definite growth of human tubercle bacilli in 0.001 mg. per cc. planting did not occur in less than six days at 37°C. This was judged by the stained smear examination of the sedimented bacilli settling in the bottom of the receptacle containing a shallow liquid medium not exceeding a depth of about one centimeter. The 0.000,001 mg. per cc. planting required up to nineteen days for discernible development or growth of the bacilli. No striking difference was noted in this submerged growth, regardless

TABLE 2

*The submerged growth of human tubercle bacilli in various liquid media*

| MEDIA  | PLANTING IN MILLIGRAMS PER CUBIC CENTIMETER |        |        |         |  |                     |         |         |         |         |
|--|---|--------|--------|---------|--|---------------------|---------|---------|---------|---------|
|  | 10 <sup>-3</sup>                            |        |        |         |  | 10 <sup>-6</sup> ** |         |         |         |         |
|  | Time after planting                         |        |        |         |  | Time after planting |         |         |         |         |
|  | 1 day                                       | 3 days | 6 days | 11 days |  | 7 days              | 12 days | 15 days | 19 days | 25 days |
| Dubos (without glycerol or Tween 80).....    | 0*  | 0      | +      | S       |  | 0                   | 0       | 0       | 0       | 0       |
| Dubos + plasma.....                          | 0   | 0      | +      | S       |  | 0                   | 0       | 0       | +       | S       |
| Dubos + serum.....                           | 0   | 0      | S      | S       |  | 0                   | 0       | 0       | S       | S       |
| Dubos + Tween 80 + glycerol + albumin V..... | 0   | 0      | +      | S       |  | 0                   | 0       | 0       | +       | +       |
| Dubos + glycerol + albumin V.....            | 0   | 0      | +      | S       |  | 0                   | 0       | 0       | S       | S       |
| Youmans.....                                 | 0   | 0      | +      | S       |  | 0                   | 0       | 0       | S       | S       |
| Youmans + plasma.....                        | 0   | 0      | +      | S       |  | 0                   | 0       | 0       | S       | S       |
| Youmans + serum.....                         | 0   | 0      | +      | S       |  | 0                   | 0       | 0       | S       | S       |
| Wong.....                                    | 0   | 0      | +      | S       |  | 0                   | 0       | 0       | +       | S       |
| Wong + plasma.....                           | 0   | 0      | +      | S       |  | 0                   | 0       | 0       | +       | S       |
| Wong + serum.....                            | 0   | 0      | S      | S       |  | 0                   | 0       | 0       | S       | S       |

\* The designations recorded on the basis of previous liquid culture studies are: 0 = no evidence of growth; + = beginning acid-fast skein formation as evidence of initial growth; S = definite acid-fast skeins. It should be noted also that the 0 does not indicate the absence of acid-fast bacilli for they may be found, and usually are, in the sediment with the heavier planting such as 10<sup>-3</sup> mg. and occasionally up to 10<sup>-6</sup> mg. per cc. planting.

\*\* The 10<sup>-8</sup> milligram planting grew only occasionally after twenty-six days at 37°C.

of whether the nutrient medium contained Tween 80, human plasma or serum, or fraction V bovine albumin, all recently advocated additions. It was noted also that whenever submerged growth occurred, a short time thereafter, in the majority of shallow liquid tubes, a fine surface film growth occurred. This was followed by the appearance of a heavier surface growth in all media tested except those containing Tween 80 which caused sufficient wetting and surface tension effects to prevent it. In all tubes and in those planted and kept in the refrigerator at 5°C., a tendency toward clumping of the bacilli and the appearance of crossed bundles of rods were noted. These phenomena appeared mostly in the



$10^{-3}$  mg. per cc. or more plantings and occasionally in the  $10^{-6}$  mg. plants of fine suspensions of human tubercle bacilli and in no wise could be confused with evidences of growth and particularly various stages of skein formation. Skeins are the ultimate proof of submerged growth if plants with fine properly prepared suspensions have been made. When submerged sediment growth occurs in the foregoing liquid media, it tends to appear as a film on the side or bottom of the glass receptacle wall and finally forms a flocculent whitish sediment, becoming more dense with time but scant in appearance and markedly so in weight compared with surface growth at all times.

In order to elaborate on the possible effects of the addition of Tween 80,<sup>3</sup> a surface tension reducing agent, especially on the growth of human tubercle bacilli, this agent, in as pure form as available from a batch approved for this type of work by Dubos, was incorporated in various concentrations into glycerol egg yolk medium. After sterilization, the media were planted with varying grades of human tubercle bacilli from 1.0 mg. to 0.000,000.01 mg. per cc. The

TABLE 3

*The effect of Tween 80 incorporated in the glycerol egg yolk medium on the growth of human tubercle bacilli*

| PERCENTAGE OF TWEEN 80 <sup>*</sup> ADDED TO GLYCEROL EGG YOLK MEDIUM | AMOUNT OF TUBERCLE BACILLI IN MILLIGRAMS PER CUBIC CENTIMETER USED FOR PLANTING |           |           |           |
|---|---|-----------|-----------|-----------|
|   | 1.0   | $10^{-3}$ | $10^{-4}$ | $10^{-5}$ |
| Control   | 2**   | 2         | 2         | 2         |
| 0.1   | 2   | 2         | 2         | 2         |
| 1.0   | 2   | 2         | 2         | 3         |
| 5.0   | 2   | 0         | 0         | 0         |

\* Dubos uses 0.02 to 0.05 per cent in the liquid medium.

\*\* The growth is graded as 0 = no growth, and a numeral indicates the number of weeks when growth first appeared.

results of the growth of the tubercle bacilli at incubator temperature are recorded in table 3.

It is noted from the results recorded in table 3 that Tween 80 does not retard the growth of human tubercle bacilli in egg yolk medium, a good nutrient, until a concentration of one per cent is reached. Then slight retardation of small plantings ( $10^{-5}$  mg.) is noticeable; and in 5 per cent, it definitely retards growth in all but heavy suspension plantings (1.0 mg. per cc.). No definite effect on colony formation of the pure Tween 80 in the amounts added to the egg yolk medium is noted. This differs from the effect of sodium taurocholate, which does alter the nature of the gross colony in that it tends to produce in higher concentration a smooth greasy type of colony.

In order to compare the results of microscopic examination of stained smears taken from liquid media (as recorded in table 2) with similar smears taken from

<sup>3</sup> The Tween 80 was obtained through the courtesy of the Atlas Powder Co., Wilmington, Delaware.

the surface of a good nutrient solid medium, a series of glycerol egg yolk cultures were planted on this medium, using graded amounts of fine suspensions of human tubercle bacilli, and smears were made and stained with the standard carbol-fuchsin (pure pararosanilin hydrochloride) method at various intervals with the same methods used for the liquid cultures. The results of these findings are recorded in table 4.

As making stained smears from the surface of good nutrient diagnostic media, such as the egg yolk medium, is not advised, it is noted that opening a culture tube for this purpose is open to criticism. In this experiment, sufficient tubes were planted to make these examinations on individual freshly-opened tubes for each test so that repetitious examination with danger of contamination and error of observation was avoided. Even though it may appear that a few days' time (up to four days) could be saved by making smears from the surface of the

TABLE 4

*The microscopic examination of stained smears from cultures of human tubercle bacilli taken from the surface of the glycerol egg yolk medium*

| INTERVAL AFTER PLANTING<br>IN DAYS | PLANTINGS OF TUBERCLE BACILLI IN MILLIGRAMS PER CUBIC CENTIMETER |           |           |
|------------------------------------|--|-----------|-----------|
|                                    | $10^{-3}$  | $10^{-6}$ | $10^{-8}$ |
| 1                                  | ⊕*   | ⊕         | 0         |
| 3                                  | ⊕  | ⊕         | 0         |
| 6                                  | ⊕  | 0         | 0         |
| 9                                  | ++   | +         | 0         |
| 13                                 | ++V  | ++V       | ++        |
| 16                                 | ++V  | ++V       | ++V       |

\* The findings from the examinations of the stained smear microscopically are recorded as 0 = no acid-fast bacilli found; ⊕ = acid-fast bacilli from the original planted suspension were found with evidence of growth or multiplication lacking; + = initiation of growth evident with beginning skein formation; ++ = definite growth with formed skeins present; V = macroscopically visible growth.

culture medium, such a procedure would appear undesirable. The saving would not be of actual material value and colony formation, which is far more important, would be sacrificed in the tube thus disturbed. An examination of the results recorded in table 4 indicates definitely that the examination of surface material by the stained smear microscopic method might lead to erroneous deductions concerning the presence of viable tubercle bacilli, for the initial seeding might be mistaken for the evidences of growth indicated by skein formation. It is also interesting that on this good nutrient solid medium definite skein formation did not precede macroscopic growth by much more than four days at most. Also it is noted that the time of macroscopic growth on a good nutrient diagnostic medium, such as the egg yolk, although slightly slower with the heavy plant ( $10^{-3}$  mg.), occurred more speedily with the smaller plantings ( $10^{-6}$  and  $10^{-8}$  mg.) than similar plantings in any of the liquid media studied (see table 2).

*The nature of submerged growth of tubercle and other acid-fast bacilli:* In order to gain a better insight into submerged growth of human tubercle bacilli and, if possible, to grow the bacilli in actual suspension in the liquid, which "submerged" and "subsurface" growth up to the present has not implied, or with which it has not succeeded, a number of experiments were performed combining solid nutrients with various nonnutrient and nutrient liquids in which the solid media were completely submerged. The results of such tests are incorporated in table 5.

The results recorded in table 5 indicate that no macroscopic growth of human tubercle bacilli, such as is regularly seen on the surface of solid nutrient media not submerged in liquids, is noted from these culture tests. It was also observed that no macroscopic growth of human tubercle bacilli occurred on the surface of the solid medium when covered with liquid, in contrast to the growth regularly seen on the surface of such solid nutrient media when they are not submerged in liquid. The submerged growth occurring in the liquid is usually found at the depth of the liquid in its lowest level as a fine flocculent sediment. In the case of the nutrients either contained in the solid medium, which diffuse into the liquid, or when the liquid itself is a nutrient for human tubercle bacilli, better submerged cultures result (within wide limits of the nutrient) and growth usually occurs shortly thereafter on the surface of the medium, particularly when egg white is present. Agar (2½ per cent) without nutrient was found to act as a definite retardant to the growth of human tubercle bacilli in good nutrient liquids in which it was submerged. So far as submerged growth is concerned from graded plantings with human tubercle bacilli, no advantages were seen from this experiment regardless of whether the liquid used above, a good nutrient solid medium, was Wong's medium, broth with glycerol and dextrose, Dubos' glycerol Tween 80, and albumin medium, or potato or egg yolk extract.

To obtain further information on submerged growth of human tubercle bacilli in a good nutrient liquid medium (Wong's), with particular reference to the site of such growth from different amounts of plants of the bacilli, especially in undisturbed tubes and with relation to the walls of the glass receptacles and the depth of the liquid medium, a number of experiments were performed with elucidating results. The results of an experiment are recorded in table 6 in which the liquid depth was varied from 1.0 cm. to 10 cm., using 1, 3, 6, and 12 cc. of Wong's glycerol dextrose medium in 15 by 125 mm. pyrex bacteriologic tubes. Readings were made after one, two, three weeks, and one and two months at 37°C. The plants consisted of human tubercle bacilli in fine suspensions containing a final concentration of 0.02 mg. per cc. of medium (the same concentration of bacilli was planted per cc. of medium without regard to volume).

It is apparent from the results recorded in table 6 that it is difficult to determine where growth started in disturbed tubes, whether on the surface or in the depth of the liquid nutrient. However, when the tubes are undisturbed and the liquid is shallow, not exceeding 1 cm. in depth, much evident growth can occur apparently earlier than surface growth following the planting of a fine suspension

TABLE 5  
*The growth of human tubercle bacilli in liquids containing completely submerged solid media*

| LIQUID COVERING MEDIA |   |                  |                           |      |                   |                  |                |                  |                  |      |                                  |                  |                                       |                  |                  |     |                  |                  |
|-----------------------|---|------------------|---------------------------|------|-------------------|------------------|----------------|------------------|------------------|------|----------------------------------|------------------|---------------------------------------|------------------|------------------|-----|------------------|------------------|
| SOLID MEDIA*          | Control—no liquid added   |                  | 5 per cent glycerol water |      | 0.9 per cent NaCl |                  | Wong Weinstein |                  | Broth            |      | Broth with glycerol and dextrose |                  | Dubos-Glycerol Tween 80 and V albumin |                  | Potato extract   |     | Egg yolk extract |                  |
|                       | Amount of tubercle bacilli in milligrams per cubic centimeter planted |                  |                           |      |                   |                  |                |                  |                  |      |                                  |                  |                                       |                  |                  |     |                  |                  |
|                       | 0.1   | 10 <sup>-1</sup> | 10 <sup>-2</sup>          | 0.1  | 10 <sup>-3</sup>  | 10 <sup>-4</sup> | 0.1            | 10 <sup>-3</sup> | 10 <sup>-4</sup> | 0.1  | 10 <sup>-3</sup>                 | 10 <sup>-4</sup> | 0.1                                   | 10 <sup>-3</sup> | 10 <sup>-4</sup> | 0.1 | 10 <sup>-3</sup> | 10 <sup>-4</sup> |
| Egg white.....        | ++  | 0                | S-Sd***                   | S-Sd | Sd                | Sd               | Sd             | Sd               | S-Sd             | S-Sd | Sd                               | 0                | S-Sd                                  | S-Sd             | Sd               | Sd  | S-Sd             | Sd               |
| Egg yolk.....         | ++  | +                | S-Sd                      | Sd   | Sd                | Sd               | Sd             | Sd               | Sd               | Sd   | Sd                               | Sd               | S-Sd                                  | Sd               | Sd               | Sd  | S-Sd             | Sd               |
| Agar.....             | 0   | 0                | 0                         | 0    | 0                 | 0                | 0              | 0                | 0                | 0    | 0                                | 0                | Sd                                    | 0                | 0                | 0   | 0                | 0                |
| Plasma.....           | +   | 0                | Sd                        | 0    | 0                 | 0                | 0              | 0                | 0                | 0    | 0                                | 0                | Sd                                    | 0                | 0                | 0   | 0                | 0                |
| Serum.....            | 0   | 0                | 0                         | 0    | 0                 | 0                | 0              | 0                | 0                | 0    | 0                                | 0                | Sd                                    | 0                | 0                | Sd  | Sd               | 0                |
| Blood.....            | +   | 0                | Sd                        | Sd   | Sd                | Sd               | Sd             | 0                | Sd               | Sd   | Sd                               | Sd               | Sd                                    | 0                | Sd               | Sd  | Sd               | Sd               |

\* None of these solid media contained glycerol, and this explains the relatively poor growth of small plantings of human tubercle bacilli on the egg yolk and blood after four weeks at 37°C. when these are recorded here. There is no practical value to readings made after this time for comparison with submerged cultures.

\*\* The growth after four weeks at 37°C. on the surface of the solids is graded from 0 = no growth to ++ = a definitely positive macroscopic growth.

\*\*\* The growth of the tubercle bacilli in the tubes containing the solid medium covered by the liquid is designated by S if a positive macroscopic surface growth developed on the liquid and Sd indicates a positive macroscopic growth below the surface of the liquid and concentrated usually at the bottom at the lowest point.

of human tubercle bacilli. On the Wong's liquid medium, the appearance of the surface growth follows shortly after the sediment growth in shallow liquid and far exceeds it in amount. In deeper undisturbed liquid, however, growth only appears on the surface of the medium, in the surface layers of liquid, and particularly in small amount on the side walls of the tube within a few cm. below the surface of the liquid, but not suspended in the liquid. The rate and grade of growth on the surface of the medium on the side walls near the surface were not affected by the amount of liquid medium in these small tubes. If the tubes were planted with only one drop of fine suspension of human tubercle bacilli containing about 1 mg. bacilli per cc., regardless whether 1 cc. to 12 cc. of medium was contained in the culture tube, the rate of growth was retarded so that the bacilli grew in the 1 and 3 cc. volumes in two weeks, the 6 cc. in three weeks, and the 12 cc. in four weeks. The explanation of the wall reaction and growth may be concerned with the presence and liberation of air from the liquid by surface

TABLE 6

*The growth of human tubercle bacilli planted in fine suspension in different volumes and depths of Wong's glycerol-dextrose synthetic liquid medium*

| VOLUME AND DEPTH OF LIQUID | DISTURBED TUBES           |         |         |          | UNDISTURBED TUBES         |         |         |          |
|----------------------------|---------------------------|---------|---------|----------|---------------------------|---------|---------|----------|
|                            | Period of growth at 37°C. |         |         |          | Period of growth at 37°C. |         |         |          |
|                            | 1 week                    | 2 weeks | 4 weeks | 2 months | 1 week                    | 2 weeks | 4 weeks | 2 months |
| 1 cc.—1 cm.....            | +*                        | +1      | +3      | +4       | +                         | +2      | +4      | +4       |
| 3 cc.—2.6 cm.....          | +                         | +2      | +3      | +4       | 0                         | 2       | 4       | 4        |
| 6 cc.—5 cm.....            | +                         | +2      | +3      | +4       | 0                         | 2       | 4       | 4        |
| 12 cc.—10 cm.....          | +                         | +2      | +3      | +4       | 0                         | 2       | 4       | 4        |

\* The growth is designated by 0 = no growth; + = sediment growth; and an added numeral from 1 to 4 indicates the grade of surface growth. The sediment growth could not be readily graded since it did not appear to increase appreciably as the time interval increased except where it apparently settled from the surface.

contact between the glass and the liquid. This seems to be a possible solution since the accumulation of air bubbles can be noted at times in tubes containing liquid media alone, but not when planted with suspensions of tubercle bacilli.

Realizing from these studies that surface tension reducing agents and liquids of low specific gravity, well below that of tubercle bacilli, can only result in a sedimentation of the bacilli, even in fine suspension primarily to the bottom of the liquid containing receptacle, means were sought to prevent this and to suspend the bacilli efficiently in a liquid to note further the effect of depth upon growth. Various means were tried including the use of serums, body fluids and salts, but none succeeded until an effort was made to find a liquid of specific gravity approximating that of moistened tubercle bacilli. It was realized that, in growing tubercle bacilli in the past on the surface of liquids, advantage had to be taken of the surface dryness of the material planted or of contained air to assist in floating these or, as sometimes performed, the bacilli were deliberately

rubbed on the glass surface at the liquid surface level and the growing bacilli would continue a phase growth there. Where large volumes of liquid were used, sediment growth did not occur. In testing the significance of specific gravity in obtaining suspended planting and growth, advantage was taken of a non-nutrient, nontoxic material designated as cellulose gum<sup>4</sup> and known chemically as sodium-methyl-carboxy-cellulose. The suitable percentage added to the Wong's nutrient medium was 6 per cent of low viscosity type in final concentra-

TABLE 7

*The suspended liquid growth of acid-fast ("Day") and human tubercle bacilli in Wong-cellulose gum-synthetic nutrient medium*

| ORGANISM                                 | ACID-FAST "DAY" BACILLUS                                      |         |  | HUMAN TUBERCLE BACILLI  |       |       |       |        |  |
|--|---|---------|--|---|-------|-------|-------|--------|--|
|  | Interval after planting and amount of surface growth at 37°C. |         | Suspended growth and depth below surface** | Interval after planting and amount of surface growth at 37°C. |       |       |       |        | Suspended growth and depth below surface** |
|  |   |         |  |   |       |       |       |        |  |
| Planting in milligrams per cc. of medium | 72 hrs.   | 96 hrs. |  | 1 wk.   | 2 wk. | 3 wk. | 1 mo. | 1½ mo. |  |
| 1  | 4*  | 4       | To 2 cm. depth                             | 0   | 1     | 2     | 3     | 3      | Turbid growth extending 2 cm.              |
| 0.1                                      | 4   | 4       | To 1.5 cm. depth                           | 0   | 1     | 2     | 2     | 3      | Turbid growth to 2 cm.                     |
| 0.01                                     | 3   | 4       | To 1.0 cm. depth                           | 0   | 0     | 1     | 1     | 2      | Turbid growth to 1 cm.                     |
| 0.001                                    | 2   | 3       | To 0.75 cm. depth                          | 0   | 0     | 1     | 1     | 2      | Turbid growth to 0.5 cm.                   |
| 0.000,1                                  | 2   | 3       | To slightly below                          | 0   | 0     | 0     | 1     | 2      | Sparse growth in clusters                  |
| 0.000,01                                 | 1   | 2       | To slightly below                          | 0   | 0     | 0     | 0     | 0      | Scattered individual colonies              |
| 0.000,001                                | 0   | 0       | Scattered colonies in the liquid           | 0   | 0     | 0     | 0     | 0      | Sparse individual colonies                 |
| 0.000,000,1                              | 0   | 0       | Scattered colonies in the liquid           | 0   | 0     | 0     | 0     | 0      | No growth discernible within 2 months      |

\* Growth on the surface of the medium is graded from 0 = no macroscopic growth; and 4 = a heavy dense growth covering the entire surface.

\*\* These studies were made with a 15 x 125 mm. bacteriological test tube which contained 6 cc. of culture medium. This gave a depth of 5 cm. of liquid in the culture tube.

tion. The cellulose gum had to be dissolved properly before adding to the Wong medium to avoid lumping and to obtain a perfectly clear medium. The results noted with this medium for obtaining suspended growth and using the acid-fast "Day" bacillus, as well as human tubercle bacilli, are recorded in table 7.

The findings recorded in table 7 indicate that suspended growth of acid-fast

<sup>4</sup> The cellulose gum was obtained through the courtesy of the Hercules Powder Company, Wilmington, Delaware.

(Day) and human tubercle bacilli is possible in a nutrient liquid medium (Wong Weinzirl) containing a nonnutrient and nontoxic cellulose gum added for increasing the suspending property of the liquid nutrient medium to a point where these bacilli will remain suspended in the liquid for an indefinite period. Although surface growth of both acid-fast and human tubercle bacilli occurs with the heavier plants of the graded plantings of fine suspensions of these bacilli, scattered submerged suspended growth occurs mainly in the smaller plantings. It is interesting also that, even though the bacilli were uniformly suspended in the liquid, growth of the suspended bacilli occurred mainly in the upper depths of the liquid in addition to the more profuse surface growth. The growth under the surface of the liquid extended to no greater depth than 2 cm., and growth at the bottom of the liquid in a depth of liquid of 5 cm. was never noted in these tests.

It appears obvious that these bacteria, usually classed as aerobes, prefer the upper liquid layers, and especially the surface of liquid nutrient media, and growth diminishes with increase in depth of liquid from the surface to 1 to 2 cm. when the air tension diminishes to such an extent in the liquid that the air requirement for the growth of these bacilli becomes inadequate. Wall reactions to glass and other solid materials must be recognized as capable of altering this somewhat. It appears also that suitable submerged suspended growth can be attained only by taking into consideration means of maintaining an adequate specific gravity and viscosity of the nutrient liquid. With the liquid media previously described, it is doubted whether submerged suspended growth has been attained even though shallow liquid was used for the purpose of obtaining successful results. Such growth as has been attained is better designated as *submerged sediment growth* in contrast to true *submerged suspended growth* attained as a result of this study.

#### SUMMARY AND CONCLUSIONS

1. As the result of a study of submerged liquid cultures of human tubercle bacilli and other acid-fast bacilli, it has become possible to develop a truly "submerged suspended" culture for these bacilli, as differentiated from the "submerged sediment" culture. The "submerged suspended" cultures were obtained by altering specific gravity and viscosity conditions rather than by the introduction of the surface tension reducing agents previously used by some investigators.

2. No significant advantage for growing tubercle bacilli in liquid cultures was noted for media containing Tween 80, plasma, or serum, over that of a simple synthetic nonprotein medium such as the Wong Weinzirl medium containing glycerol and dextrose.

3. Tween 80, added to a good nutrient medium, such as the egg yolk medium suited to growing small plants of acid-fast and human tubercle bacilli, was found to be toxic to these bacilli only when amounts exceeding one per cent were used in the medium.

4. The microscopic examination of the stained smear to determine the growth

of human tubercle bacilli did not reveal any particular advantages over careful macroscopic observation when a good nutrient solid medium was used. Furthermore, it was encumbered by a technique which might lead to erroneous deductions for practical clinical purposes. Likewise, the use of submerged liquid cultures, as suggested by Kirschner, Dubos, and Youmans' studies, did not show any particular advantages when quantitative planting tests were compared with those noted on solid nutrient diagnostic media such as the egg yolk medium. Also, the submerged liquid cultures have many disadvantages in practice and are not advised for diagnostic purposes at the present time.

5. It is doubted whether findings obtained with submerged cultures of human tubercle bacilli in liquid media are more readily translated into *in vivo* values, as suggested by Kirschner some time ago, than are the appropriately evaluated and tested surface cultures on solid media. Both require careful evaluation and can be interpreted only as playing a small part in the complicated picture of the growth of tubercle bacilli *in vivo* or the development of tuberculosis. Any deductions from cultures alone should be guardedly evaluated.

6. For the present, it would appear advisable to continue the use of good nutrient solid media for the bacteriologic diagnosis of tuberculosis, rather than to rely on the findings with liquid culture media which must of necessity depend on the finding of acid-fast bacilli and are not as delicate nor as expeditious in use as are the solid media.

#### SUMARIO Y CONCLUSIONES

##### *Cultivos Líquidos Suspendidos Sumergidos del M. Tuberculosis y de otros Bacilos Ácidorresistentes bajo el Influjo de Factores Físicos y Químicos*

1. Como fruto del estudio de cultivos líquidos sumergidos de bacilos tuberculosos humanos y otros bacilos ácidorresistentes, ha sido posible elaborar un cultivo verdaderamente "sumergido y suspendido" de dichos bacilos, distinto del cultivo en sedimento sumergido. Los cultivos "suspendidos sumergidos" fueron obtenidos alterando las condiciones de densidad y viscosidad, más bien que introduciendo los reductores de la tensión superficial previamente utilizados por otros investigadores.

2. No se notó ninguna ventaja significativa cultivando los bacilos tuberculosos en forma líquida en medios que contenían Tween 80, plasma o suero, comparados con un simple medio no proteico sintético, tal como el de Wong Weinzirl, que contiene glicerol y dextrosa.

3. El Tween 80, agregado a un buen medio nutriente, tal como el medio de yema de huevo apropiado para cultivar plantillas de bacilos tuberculosos humanos y ácidorresistentes, sólo resultó tóxico para dichos bacilos cuando se empleaba en el medio en proporciones superiores a uno por ciento.

4. El examen microscópico de los frotos teñidos para determinar la proliferación de los bacilos tuberculosos humanos no reveló mayor ventaja sobre la cuidadosa observación macroscópica cuando se usaba un buen medio sólido nutriente. Además, lo grave una técnica que podría conducir a deducciones erróneas para fines clínicos prácticos. Tampoco mostró mayor ventaja el empleo de cultivos



líquidos sumergidos, según propusieran en sus estudios Kirschner, Dubos, y Youman, al comparar los ensayos de siembras cuantitativas con las notadas en medios nutrientes sólidos de diagnóstico, tales como el de yema de huevo. Además, los cultivos líquidos sumergidos adolecen de muchas desventajas en la práctica y no se recomiendan para fines de diagnóstico por ahora.

5. Dúdase que los hallazgos obtenidos con cultivos sumergidos se traduzcan más fácilmente en valores *in vivo*, según indicara Kirschner hace algún tiempo, que los de los cultivos superficiales en medios sólidos, debidamente evaluados y comprobados. Ambos exigen valuación cuidadosa y pueden interpretarse como desempeñando puramente un pequeño papel en el complicado cuadro del crecimiento de los bacilos tuberculosos *in vivo* o la aparición de tuberculosis. Toda deducción basada exclusivamente en los cultivos debe ser justipreciada cautelosamente.

6. Por el momento, parece prudente continuar usando buenos medios sólidos nutrientes para el diagnóstico bacteriológico de la tuberculosis, más bien que atenerse a los hallazgos derivados de medios líquidos, que tienen forzosamente que basarse en el descubrimiento de bacilos ácidosresistentes en medios que no son tan delicados ni tan expeditos para empleo como los medios sólidos.

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# THE EFFECT OF PHENYLHYDRAZINE IN EXPERIMENTAL TUBERCULOSIS<sup>1,2</sup>

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## INTRODUCTION

The chemotherapy of tuberculosis has developed into a confusing and complicated subject, as evidenced by the numerous and inconclusive new conceptions which are based on trivial and frequently inconsequential observations recorded without consideration of the mechanisms involved in such actions. Added to this is the incrimination of such features as have evolved around the antibiotics particularly, which, though chemotherapeutic agents in the broader sense, appear to act primarily as retardants *in vitro* and are then assumed to act in the same way *in vivo* on an *a priori* basis. Whether the latter deduction can be drawn directly regarding these agents requires further elucidation. It is evident, however, that the intelligent application of any therapeutic agent must be based on a full understanding of the mechanism involved in its action and a proper interpretation of its effects on tuberculosis. These criteria must be determined by exacting studies which utilize a reliable and clearly defined knowledge of all the vagaries of the tubercle bacillus and experimental tuberculosis, as well as the naturally occurring infection of man. In this respect, and this respect only, the modern chemotherapy of tuberculosis differs from that of decades ago. Thus a revaluation of certain agents may be essential especially in the light of the newer methods, newer knowledge, and the newer interpretation of tuberculosis; and the study of the antibiotics has added to this materially.

The study of even experimentally produced tuberculosis is confused by the use of methods which lead to markedly variegated results. These are seen particularly when intracutaneous or subcutaneous methods of infection are applied even to the highly susceptible guinea pig. It was for this reason that Koch, in his early tuberculin testing work, resorted to the use of large numbers of guinea pigs in order to obtain animals suitable for such testing. From the use of these tests, elaborate charted systems of organic involvement have developed which are time-consuming to the reader and add little to the interpretation of the ultimate results. In an effort to obviate this as far as possible and to simplify chemotherapeutic testing, it was found that the use of the intravenous injection technique, introduced in 1945 (1), proved invaluable for the interpretation and evaluation of chemotherapeutic and antibiotic agents. The intravenous method also added the criterion of lethal effects from tuberculosis which could not be defined accurately by other methods and, although apparently drastic, made chemotherapeutic effects evident speedily and decisively (2, 3). It is evident from previous studies that tuberculosis of the guinea pig as a whole, or of any particular animal species, including man, is affected by a great many factors, some

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of which are conspicuous and some, almost insignificant. These factors determine the outcome of an infection with tubercle bacilli in regard to amount and virulence of organisms, and are markedly variegated as the time factor increases. In some species, including man, the time factor looms large and the persistence of viable bacilli is almost indefinite, death being the consummation of innumerable factors, sometimes even trivial ones when viewed independently. To obviate this, certain set laboratory conditions for experimental purposes must be met. Likewise, in an appropriate experimental setup, tuberculous involvement, under not too protracted conditions, can prove of significant value. . Cautious interpretation makes it appear desirable to study agents which apparently act on the same general mechanisms, but which act profoundly differently on tuberculosis.

In 1945 (1) it was reported that diasone and the sulfone drugs acted indirectly on tuberculosis in the guinea pig by affecting the oxygen mechanism in the body of this animal in a way which could not be duplicated practically in man.

In 1929 Kuroya (4) and Aoki (5) studied the aromatic amines and hydrazine drugs, and phenylhydrazinehydrochloride in particular, because of their tuberculostatic action *in vitro*. With a recognition of their ability to produce marked anemia, they state, "accompanying the proliferation of myeloid and erythropoietic cells of the bone marrow, myeloid metaplasia and erythropoiesis in the spleen, liver and lymph nodes of experimental animals, and at the same time brings about the hyperplasia of the reticuloendothelial system. . . . And the reticulo-endothelial system plays an important role in the formation of the tubercle." They note "the anemia caused by these substances may not be the primordial factor, but the substances themselves may be the principle factor," suggesting a direct chemical retardant action on the tubercle bacilli as significant in the effect obtained. The tuberculosis in the phenylhydrazinehydrochloride (large doses) injected animals was distinctly milder than that of the controls. Small doses of phenylhydrazinehydrochloride were not successful in showing this effect. On the other hand, repeated bleeding of the guinea pigs ("causing oligocythaemia and erythropoiesis like phenylhydrazine but the mechanism of action differing") exerted no influence on the tuberculosis. Sollmann (6) points out that phenylhydrazinehydrochloride produced blood picture changes advancing to pronounced anemia. It has little effect on hematopoiesis, causes hyperplasia of the spleen and slight hyperplasia of the leukoblastic elements of the bone marrow, but it has no primary effect on the erythroblastic elements nor on the platelets, and the reticulocytes tend to increase. The anemia essentially is caused by hemolysis of the mature red cells.

In view of this observed apparent effect on the tuberculosis and on the animals' blood systems, it was considered advisable to attempt a verification and elaboration of these findings. Accordingly, phenylhydrazinehydrochloride, as a typical example of this group of chemicals, was studied both *in vitro* and *in vivo* for its effect upon the tubercle bacilli and experimental tuberculosis, bearing in mind the experiences with recent chemotherapeutic and antibiotic agents and applying specially developed test methods.

## MATERIALS AND METHODS

A chemically pure phenylhydrazinehydrochloride (Eastman Kodak Company) was used for all the following observations. Because of the recent stress placed on retardant action (bacteriostasis) rather than the tuberculocidal action emphasized in chemotherapeutic studies of several decades ago, the phenylhydrazinehydrochloride was added to a simple nonprotein synthetic medium in varying amounts. Acid-fast saprophytes and human tubercle bacilli were then planted and growth at incubator temperature (37°C.) noted, with the results recorded in table 1.

## EXPERIMENTAL OBSERVATIONS

It is evident from the findings recorded in table 1 that phenylhydrazinehydrochloride is a definite retardant to both an acid-fast saprophyte and the human tubercle bacillus. Concentrations of 0.05 mg. per cc. retarded growth in a simple synthetic nonprotein nutrient medium. This medium is usually con

TABLE 1

*Effect of phenylhydrazinehydrochloride on the growth of an acid-fast saprophyte and the human tubercle bacillus planted in a simple synthetic nonprotein medium (Wong-Weinzirl)*

| AMOUNT OF PHENYLHYDRAZINEHYDRO-<br>CHLORIDE ADDED IN MG. PER CC.<br>OF MEDIUM | TYPE OF TEST ORGANISMS (0.02 MG. PER CC.) PLANTED |                        |
|---|---|------------------------|
|   | Acid-fast saprophyte ("Day")                      | Human tubercle bacilli |
| Control 0   | +++* (in 2 days)                                  | +++ (in 3 weeks)       |
| 0.005   | +++ (in 2 days)                                   | + (in 4 weeks)         |
| 0.01  | + (in 2 days)                                     | + (in 6 weeks)         |
| 0.05  | 0 (after 4 days)                                  | 0 (after 8 weeks)      |

\* The amount of growth is indicated as 0 = no visible growth, to +++ = a heavy growth covering the surface of the medium.

sidered to be a relatively poor nutrient requiring heavy plantings of these bacilli to obtain a successful growth. The retardant concentration of phenylhydrazinehydrochloride also compares favorably in value with such tuberculostatic antibiotics as streptomycin, which give a retardant value in plain broth of 0.001 mg. per cc., considered the standard unit of streptomycin, while the amount required to retard in the same synthetic medium used in these tests and with the same plantings of these bacilli is five to ten times as much, or about 0.01 mg. per cc. (7). With this in mind, it becomes evident that from the retardant value *in vitro* it might be expected that a retardant effect upon tuberculosis *in vivo* is a possibility. In view of the fact that the toxicity of phenylhydrazine is complicated by the factors of blood and organic effects, a direct analysis of an *in vivo* retardant action becomes markedly complicated. For this reason, the *in vivo* effects of phenylhydrazinehydrochloride were studied by initiating the treatment with small doses (2.5 mg. per 300 gram animal by subcutaneous injection of a watery solution) and gradually increasing this to about 15 mg. per animal, which approximated the maximum tolerated dose. The purpose

primarily was to reduce the erythrocyte count and maintain it at approximately the three million per cu. mm. level, below which amount the guinea pigs usually succumb to the fatal effects of the phenylhydrazinehydrochloride.

TABLE 2

*The effect of phenylhydrazinehydrochloride on the tuberculosis produced by the intravenous injection of 1.0 mg. virulent human tubercle bacilli*

| GUINEA PIG      | ERYTHROCYTE COUNT AT START PER CU. MM. | ERYTHROCYTE COUNT THREE WEEKS AFTER TREATMENT PER CU. MM. | DEATH IN DAYS** | WEIGHT OF SPLEEN IN GRAMS |
|-----------------|--|---|-----------------|---------------------------|
| Control 1.....  |  |   | 20              | 6.5                       |
| Control 2.....  |  |   | 23              | 2.2                       |
| Control 3.....  |  |   | 23              | 2.7                       |
| Control 4.....  |  |   | 23              | 3.9                       |
| Control 5.....  |  |   | 26              | 4.8                       |
| Treated* 1..... | $5.73 \times 10^6$                     | $2.59 \times 10^6$  | 18              | 13.9                      |
| Treated 2.....  | $6.30 \times 10^6$                     | $3.55 \times 10^6$  | 20              | 8.8                       |
| Treated 3.....  | $7.28 \times 10^6$                     | $2.81 \times 10^6$  | 20              | 7.4                       |
| Treated 4.....  | $6.67 \times 10^6$                     | $2.74 \times 10^6$  | 21              | 8.5                       |
| Treated 5.....  | $6.47 \times 10^6$                     | $3.25 \times 10^6$  | 22              | 3.7                       |

\* These guinea pigs were started on treatment two weeks before infection with 2.5 mg. phenylhydrazinehydrochloride and the treatment dose was increased every other day until the maximum of 15 mg. was attained after about two weeks. The animals were then maintained at this low erythrocyte level throughout infection with lesser and appropriate doses of phenylhydrazinehydrochloride.

\*\* All the guinea pigs revealed a pulmonary miliary tuberculosis at the time of death.

TABLE 3

*The effect of phenylhydrazinehydrochloride treatment on tuberculosis in the guinea pig*

| GUINEA PIG | ERYTHROCYTE COUNT PER CU.MM. BEFORE INFECTING | ERYTHROCYTE COUNT PER CU.MM. ONE WEEK AFTER INFECTION | DAYS AFTER INFECTION WHEN GUINEA PIG DIED* | WEIGHT OF SPLEEN IN GRAMS |
|------------|---|---|--|---------------------------|
| 1          | $6.15 \times 10^6$                            | $1.65 \times 10^6$                                    | 8  | 4.8                       |
| 2          | $5.24 \times 10^6$                            | $2.03 \times 10^6$                                    | 9  | 3.5                       |
| 3          | $6.92 \times 10^6$                            | $1.83 \times 10^6$                                    | 10   | 5.1                       |
| 4          | $6.56 \times 10^6$                            | $2.00 \times 10^6$                                    | 14   | 12.0                      |
| 5          | $5.21 \times 10^6$                            | $1.96 \times 10^6$                                    | 16   | 10.0                      |

\* The controls noted in table 2 apply here also. These guinea pigs were given 15 mg. of phenylhydrazinehydrochloride coincident with infection and every other day for one week and then at weekly intervals until death. All the animals treated were profoundly jaundiced.

Phenylhydrazinehydrochloride treatment was tried in a number of different dosages and at different intervals of infection. The results of some of these findings are recorded in tables 2 and 3. In all cases, the animals were carefully controlled for phenylhydrazinehydrochloride action by repeated erythrocyte counts at three day intervals.

An examination of the results recorded in table 2 indicates fairly definitely that the cautious use of phenylhydrazinehydrochloride in amounts affecting the erythrocytes, as indicated by the erythrocyte count in the animals used for test, is without appreciable effect upon either the anatomical tuberculous involvement of the organs or upon the life duration of the guinea pigs after intravenous infection with virulent human tubercle bacilli. The average duration of life of the control animals was twenty-three days, while that of the phenylhydrazinehydrochloride-treated animals was twenty days. The erythrocytes had been reduced about one-half by the drug treatment, and the spleen had increased in the infected-treated animals to 8.5 grams, in contrast to an average splenic weight of 4.0 grams for the untreated infected controls. This splenomegaly in itself served to mask the tuberculosis in the spleen and may under certain circumstances lead to erroneous deductions. It is evident also from this and similar experiments performed with phenylhydrazinehydrochloride that the mechanism of action differs materially from that of the sulfonamide and sulfone drugs, including diasone, and may be assumed to stress the importance of the intimate action of each on the blood and oxygenating mechanism of the animal body and its compensatory powers. Phenylhydrazinehydrochloride is definitely an erythrocytic poison, while the sulfonamide and sulfone drugs only affect this system in a less drastic manner, acting primarily on the oxygenating mechanisms directly.

In the hope of obtaining a retarding effect on the tubercle bacillus directly, an additional experiment was performed, using larger doses of phenylhydrazinehydrochloride by subcutaneous injection. It became evident, however, that no such effect could be obtained, as is illustrated in table 3, which also contains data disclosing the resulting profound organo-toxic and lethal action of the drug.

It appears from the results recorded in table 3 that phenylhydrazinehydrochloride is too toxic to be able to attain a retardant concentration toward the tubercle bacillus in the body. It further appears that the toxic organic and blood effects of the drug are not of significance, even though profound, so far as affecting either the tubercle bacillus or tuberculosis *in vivo* are concerned. The marked splenomegaly noted is an effect on the entire hemosplenic system and differs decidedly from that of the sulfonamide and sulfone drugs, particularly diasone, as well as the effects of certain antibiotics such as streptomycin. The short duration of this experiment and profound organic effects with consequent marked jaundice are to be attributed primarily to the phenylhydrazinehydrochloride action and not to the tuberculosis.

#### SUMMARY AND CONCLUSIONS

The recent scientific interest in the action of sulfonamide and sulfone drugs, as well as the retardant antibiotics, upon tuberculosis has renewed the desire for an explanation of the mechanism involved in such effects as are seen particularly in experimental animals where controlled tests can be performed. Phenylhydrazinehydrochloride comes in the category of a drug possessing specific

effects upon the erythrocytic system with the production of a definite hemolytic anemia and exerts as well a retardant *in vitro* effect upon the growth of acid-fast saprophytes and human tubercle bacilli. Therefore, it appeared desirable to study the reputed retardant effect of phenylhydrazinehydrochloride on experimentally controlled animal tuberculosis, using methods emphasized as a result of the recent advances made in the study of the antibiotics. Contrary to previous reports, phenylhydrazinehydrochloride, though producing a definite hemolytic anemia and specific organic changes in the guinea pig, was not capable of retarding the tuberculosis in this animal, nor did it delay the lethal effect of virulent human tubercle bacilli introduced intravenously. However, the splenomegaly resulting from the phenylhydrazinehydrochloride treatment may mask the tuberculosis normally appreciable at postmortem in this organ. These observations also point to a difference in the mechanisms involved in the chemotherapeutic and antibiotic actions on tuberculosis particularly discernible for the different groups of chemical substances.

#### SUMARIO Y CONCLUSIONES

##### *El Efecto de la Fenilhidracina en la Tuberculosis Experimental*

El interés científico despertado recientemente en la acción de los sulfonamidos y las sulfonas, así como en la de los antibióticos retardadores, sobre la tuberculosis ha renovado el deseo de encontrar una explicación del mecanismo que interviene en los efectos observados en particular en los animales de experimentación en los que pueden ejecutarse ensayos comprobados. El clorhidrato de fenilhidracina figura en la categoría de las drogas que muestran efectos específicos sobre el aparato eritrocitario, produciendo una anemia hemolítica bien definida, a la vez que ejercen efecto retardador *in vitro* sobre la proliferación de los saprofitos ácidosresistentes y los bacilos tuberculosos humanos. Por lo mismo, pareció conveniente estudiar el supuesto efecto retardador del clorhidrato de fenilhidracina sobre la tuberculosis experimentalmente comprobada en los animales, utilizando las técnicas puestas de relieve por los recientes adelantos logrados en el estudio de los antibióticos. En contraposición a previas comunicaciones, el clorhidrato de fenilhidracina, aunque produciendo anemia hemolítica bien definida y patología orgánica específica en el cobayo, no se mostró capaz de retardar la tuberculosis en dicho animal, ni tampoco demoró el efecto letal de los bacilos tuberculosos humanos introducidos endovenosamente. No obstante, la esplenomegalia resultante del tratamiento con clorhidrato de fenilhidracina puede enmascarar la tuberculosis normalmente apreciable en la autopsia en el bazo. Estas observaciones también señalan una diferencia entre los mecanismos que intervienen en las acciones quimioterapéutica y antibiótica sobre la tuberculosis, diferencia esta en particular discernible para los diversos grupos de sustancias químicas.

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# TUBERCULOSIS IN THE FEEBLEMINED<sup>1</sup>

PETER A. THEODOS<sup>2</sup>

The associated physical inferiority in the mentally defective has made the problem of tuberculosis in institutions for the feeble-minded a most important one. Many investigators (1, 2, 3) have commented on the excessive mortality and morbidity from pulmonary tuberculosis and most agree that the death rate is four to seven times higher in the mentally defective than it is in the nondefective population.

This fact was borne out by an investigation of the causes of death during the years 1932 to 1938 at the Pennhurst State School for the Feeble-minded. In this large state institution, containing 2,400 beds devoted to the study, care, treatment and education of mentally defective boys and girls, it was found that, on an average each year, 28.4 per cent of deaths were caused by tuberculosis.

In order to study the problem in detail and to segregate the active cases of pulmonary tuberculosis which acted as foci of infection, a survey of the entire institution was carried out in 1938 and 1939. The work was interrupted during the war years, but was subsequently resumed.

The present report deals with the findings of the original survey, the present status of the then diagnosed cases, and an account of new cases which have developed in the interim.

The original survey was done at a time when mass miniature radiological examinations had not attained the widespread use which they now enjoy. In the absence of such facilities at that time, recourse was made to the conventional procedures of tuberculin testing, with roentgenologic studies of all positive reactors. A first dose of 0.01 mg. of Old Tuberculin was given, using the Mantoux technique. Those who reacted negatively were given a second dose of 0.1 mg. A chest roentgenogram of each positive reactor was obtained, and, if any suspicious findings were present, the patient was hospitalized for a complete clinical study. All patients whose sputum contained tubercle bacilli, as well as those without tubercle bacilli in the sputum, whose roentgenologic or clinical findings suggested the presence of active tuberculosis, were isolated in the hospital section for appropriate treatment.

## FINDINGS OF SURVEY IN 1938 TO 1939

A total of 1,733 patients were intensively studied. Of these, 1,415, or 81.6 per cent, reacted positive to either the 0.01 or 0.1 mg. dose of Old Tuberculin and 307 (17.8 per cent) were negative to both strengths. The remaining 11 cases were not tested as they were manifest active cases of tuberculosis. These findings are in close agreement with those of Burns (4), but higher than in Bronfenbrenner's series (5).

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The high percentage of positive reactors found is in keeping with the expected high prevalence of tuberculous infection among mental defectives when one considers the mortality figures from pulmonary tuberculosis in the institutions. This is in marked contrast to the incidence of tuberculous infection in the population in general. A State institution for the feeble-minded might well be considered as a community in itself. When compared with comparable groups elsewhere, such as a city community or a public school, a marked difference in the incidence of infection is at once noted. Hetherington et al. (6) found 44.0 per cent positive reactors in the school children of Philadelphia, using the Mantoux test (0.01 mg.) and Harrington and Myers (7) found 36.6 per cent

TABLE 1  
*Incidence of positive reactors in relation to the mental status*

| STATUS          | TESTED | POSITIVE REACTORS | PER CENT |
|-----------------|--------|-------------------|----------|
| Idiots.....     | 431    | 389               | 90.2     |
| Imbeciles.....  | 839    | 682               | 81.2     |
| Morons.....     | 425    | 316               | 74.3     |
| Borderline..... | 38     | 28                | 73.7     |
| All Grades..... | 1,733  | 1,415             | 81.6     |

TABLE 2  
*Duration of hospital stay*

| STATUS          | POSITIVE REACTORS | AVERAGE STAY | NEGATIVE REACTORS | AVERAGE STAY |
|-----------------|-------------------|--------------|-------------------|--------------|
|                 |                   | <i>years</i> |                   | <i>years</i> |
| Idiots.....     | 389               | 13.1         | 42                | 5.6          |
| Imbeciles.....  | 682               | 14.3         | 157               | 3.7          |
| Morons.....     | 316               | 10.7         | 109               | 2.8          |
| Borderline..... | 28                | 6.2          | 10                | 2.9          |

reactors in a similar study in Minneapolis. Other studies vary from a low of 16.4 per cent to a high of 64.6 per cent (8, 9, 10, 11).

Analysis of the components of table 1 shows that tuberculous infection is more prevalent in the lower grade patients, that is, in inverse ratio to the mental status. This would indicate that mental defect in itself is a factor favoring the spread of tuberculous infection.

In table 2 may be seen the length of time the positive and negative reactors had been in the institution at the time of testing. It can be seen that the duration of stay is on an average 5.2 per cent years longer in the lower two grades, where the rate of infection is greater, than in the higher two grades where the infection rate is low. Similarly, the length of stay of the negative reactors is much less than of the positive reactors. With increase in stay, the opportunities for intramural infection are greater and it may be this fact which explains the

greater incidence of infection in the lower grade patients rather than increased susceptibility.

Analysis in reference to the chronological age (table 3) shows that incidence of tuberculous infection increases in direct proportion to the age, being higher in the older age groups. This bears out the usual tendency of tuberculous infection to increase in its prevalence with advancing age. This phenomenon has been noted by a number of investigators (5, 6, 7) including Morse (12) who found twice as many positive reactors among high school students as among grade school pupils.

Of the 1,415 patients who were tuberculin positive, a total of 142, or 8.2 per cent of the total group surveyed (1,733), were found to have lesions characteristic of the reinfection type of pulmonary tuberculosis. This included the lesions considered as healed or arrested and those which were clinically significant. Excluded from consideration is a group of 31 cases showing suspicious roent-

TABLE 3  
*Incidence of positive reaction at various chronological ages*

| MENTAL STATUS | AGE PERIODS IN GROUPS |          |          |        |          |          |        |          |          |        |          |          |        |          |          |        |          |          |
|---------------|-----------------------|----------|----------|--------|----------|----------|--------|----------|----------|--------|----------|----------|--------|----------|----------|--------|----------|----------|
|               | 0-10                  |          |          | 11-20  |          |          | 21-30  |          |          | 31-40  |          |          | 41-50  |          |          | 51-60  |          |          |
|               | Tested                | Reactors |          | Tested | Reactors |          | Tested | Reactors |          | Tested | Reactors |          | Tested | Reactors |          | Tested | Reactors |          |
|               |                       | Number   | Per cent |        | Number   | Per cent |        | Number   | Per cent |        | Number   | Per cent |        | Number   | Per cent |        | Number   | Per cent |
| Idiots.....   | 6                     | 4        | 66       | 179    | 160      | 89       | 149    | 139      | 93       | 71     | 67       | 94       | 15     | 15       | 100      | 4      | 4        | 100      |
| Imbeciles...  | 9                     | 6        | 66       | 276    | 183      | 66       | 286    | 258      | 90       | 184    | 168      | 91       | 66     | 61       | 92       | 7      | 6        | 85       |
| Morons.....   | 1                     | 0        | 0        | 173    | 94       | 54       | 165    | 148      | 89       | 55     | 47       | 85       | 30     | 26       | 87       | 2      | 1        | 50       |
| Borderline..  | 1                     | 1        | 100      | 17     | 8        | 49       | 10     | 10       | 100      | 6      | 6        | 100      | 3      | 3        | 100      | 1      | 0        | 0        |
| All ages..    | 17                    | 11       | 65       | 645    | 445      | 69       | 610    | 555      | 91       | 316    | 288      | 91       | 114    | 105      | 92       | 14     | 11       | 80       |

genologic shadows which have been considered as probable healed tuberculosis of the reinfection type. By a clinically significant lesion is meant one of the reinfection type which required of the patient some modification of his mode of living ranging from immediate hospitalization to slight reduction of physical activity and periodic observation. These lesions, therefore, varied from those obviously active, with associated constitutional symptoms and abnormal physical findings, to those without clinical evidence of activity the stability of which could not be determined without subsequent reexamination. Pathologically, these lesions presumably included the exudative, exudative-productive, caseous pneumonic, and productive types (13). In most cases the diagnosis was based entirely on the roentgenologic findings, particularly in the lower grade patients where physical examinations were very difficult and unreliable.

Of the 142 lesions, 77, or 54.2 per cent, were clinically significant and 65, or 45.8 per cent, were healed cases. For the total survey group, this makes a total

of 4.4 per cent clinically significant lesions and 3.8 per cent considered to be healed. These findings are somewhat higher than in Burns' series (4) in which he found an incidence of 2.1 per cent significant lesions. Hamer and Wentzel (14) in the Netherlands detected a more or less active pulmonary process in 3.1 per cent of their series of 687 inmates.

When compared with the findings in surveys among normal people (15, 16, 17), this relatively high incidence becomes readily apparent. Bloch and his associates (15), on the basis of an extensive review of the literature, both of this country and abroad, tabulated figures covering over a million examinations taken on various cross sections of an apparently healthy population. These workers estimated that about 1.5 per cent of the adult population have active pulmonary tuberculosis.

Of the 77 patients with clinically significant lesions, there were 24, or 31.2 per cent, who were discharging tubercle bacilli as determined by direct smear or concentrate of the sputum, or by examination of the gastric contents (table 4). All of these patients except one were among the group classed as far advanced. In table 4 may also be seen the extent of the disease at the time of diagnosis.

TABLE 4

*Status of sputum and extent of disease in the clinically significant cases*

|                                 | NUMBER | MINIMAL | MODERATELY<br>ADVANCED | FAR ADVANCED |
|---------------------------------|--------|---------|------------------------|--------------|
| Cases with positive sputum..... | 24     | —       | 1                      | 23           |
| Cases with negative sputum..... | 53     | 22      | 21                     | 10           |
| Total.....                      | 77     | 22      | 22                     | 33           |

Approximately 70 per cent were in the moderately or far advanced stage when discovered. This is in contrast to Butler's (18) study in California in which slightly more than 50 per cent of his cases were in these advanced categories. In the healed group of the present study, 47 were classed as minimal and 12 as moderately advanced. These lesions presumably were of the productive or fibroid type which gave rise to no symptoms and no abnormal laboratory findings.

The greater number of active cases (89.6 per cent) and healed cases (74 per cent) was found in patients in the two lower grades (table 5). These findings were to be expected in view of the high incidence of tuberculin sensitivity in these groups (table 1). Moreover, it has been observed prior to the survey that the major portion of those ill with clinical tuberculosis were residents of the lower grade wards. The rate varies in direct proportion to the degree of mental defect, being highest in the idiots and least in the borderline cases. In fact, the incidence in the higher grade patients is more or less parallel to that found in the extramural population.

The extent of the disease in the various mental age groups may be seen in table 6. In each case more far advanced lesions were discovered than either

minimal or moderately advanced. This is undoubtedly due to the difficulty of early diagnosis in low grade patients without frequent routine roentgenologic examination.

In the group of 1,415 tuberculin positive cases which were examined roentgenologically, a total of 595, or 42 per cent, showed a healed primary lesion as indicated by calcium deposits in the hilar areas or a Ghon focus. Of these, there were 69 cases (4.8 per cent) with a demonstrable healed Ghon focus in the paren-

TABLE 5

*Incidence of significant lesions in the various mental groups*

|                 | NUMBER TESTED | ACTIVE LESIONS |          | HEALED LESIONS |          |
|-----------------|---------------|----------------|----------|----------------|----------|
|                 |               | Number         | Per cent | Number         | Per cent |
| Idiots.....     | 431           | 36             | 8.3      | 23             | 5.3      |
| Imbeciles.....  | 839           | 33             | 3.9      | 34             | 4.0      |
| Morons.....     | 425           | 8              | 1.9      | 7              | 1.6      |
| Borderline..... | 38            | 0              | 0        | 1              | 2.7      |

TABLE 6

*Extent of lesions in various mental age groups*

|             | TOTAL | MINIMAL |          | MODERATELY ADVANCED |          | FAR ADVANCED |          |
|-------------|-------|---------|----------|---------------------|----------|--------------|----------|
|             |       | Number  | Per cent | Number              | Per cent | Number       | Per cent |
| Idiot:      |       |         |          |                     |          |              |          |
| Active..... | 36    | 13      | 36       | 9                   | 25       | 14           | 39       |
| Healed..... | 23    | 19      | 83       | 4                   | 17       | —            | —        |
| Imbecile:   |       |         |          |                     |          |              |          |
| Active..... | 33    | 7       | 21       | 11                  | 33       | 15           | 46       |
| Healed..... | 34    | 29      | 90       | 5                   | 10       | —            | —        |
| Moron:      |       |         |          |                     |          |              |          |
| Active..... | 8     | 1       | 17       | 1                   | 17       | 6            | 66       |
| Healed..... | 7     | 5       | 71       | 2                   | 29       | —            | —        |
| Borderline: |       |         |          |                     |          |              |          |
| Active..... | —     | —       | —        | —                   | —        | —            | —        |
| Healed..... | 1     | 1       | 100      | —                   | —        | —            | —        |

chyma. Only 5, or 0.35 per cent, were diagnosed as having active primary type tuberculosis which required hospitalization and observation.

Five cases of osteal tuberculosis were found; three of the spine and one each of the hip and elbow. Pleurisy with effusion was found in only two cases.

The family history of the 1,415 patients intensively studied revealed a known family incidence of tuberculosis in 7.2 per cent and of mental disease in 41.0 per cent. These figures are probably conservative as many of the case records were inadequate in detail as regards the past history of the patients.

## PRESENT STATUS OF THE CASES DETECTED IN 1938 TO 1939

The survey work at Pennhurst was interrupted during the war years but has now been resumed. In table 7 may be seen the present status of these patients as determined on roentgenologic and clinical evaluation seven years later. It can be seen that slightly more than 50 per cent of the active cases are now dead from the progression of the disease. In 60 per cent of the cases, death occurred within two years after detection of the tuberculosis. As was to be expected, the death rate was largest (81.8 per cent) in the cases originally diagnosed as far advanced. In the healed category, 16 out of the 65 cases (25 per cent) have either died or become active, emphasizing again the necessity of continued observation of any case diagnosed as healed. Of the active primary cases, 4 have died; one of a tuberculous meningitis, another of a progressive primary complex, and the other 2 of nontuberculous causes. The fifth patient now has a healed primary complex.

TABLE 7  
*Status of diagnosed cases seven years after survey*

|   | ACTIVE CASES |              |             | HEALED CASES |              | ACTIVE<br>PRIMARY<br>TUBER-<br>CULOSIS | EXTRA-<br>PULMONARY<br>TUBER-<br>CULOSIS | PLEURISY<br>WITH<br>EFFUSION |
|---|--------------|--------------|-------------|--------------|--------------|--|--|------------------------------|
|   | Min.         | Mod.<br>adv. | Far<br>adv. | Min.         | Mod.<br>adv. |  |  |                              |
| Status, 1938 to 1939.....                     | 22           | 22           | 33          | 56           | 9            | 5                                      | 5  | 2                            |
| Status 1946:                                  |              |              |             |              |              |  |  |                              |
| Dead.....                                     | 6            | 7            | 27          | 7            | 1            | 2                                      | 1  | 2                            |
| Worse.....                                    | 3            | 3            | —           | 4            | 4            | —                                      | —  | —                            |
| No change.....                                | —            | 1            | —           | 27           | —            | —                                      | 3  | —                            |
| Improved.....                                 | 10           | 8            | 6           | —            | —            | 1                                      | —  | —                            |
| Discharged or death from<br>other causes..... | 3            | 3            | —           | 18           | 4            | 2                                      | 1  | —                            |

Both patients with pleural effusion have died as a result of the subsequent development and progression of active tuberculous disease. Of the 5 cases of extrapulmonary tuberculosis, one has died of tuberculous meningitis complicating a tuberculous spondilitis.

As a matter of interest the group of 38 cases diagnosed as probably healed tuberculosis was also examined. Of these, 7, or 18 per cent, have developed active reinfection type of disease, a much higher incidence than the patient population in general. This probably means that a goodly percentage of the cases actually had significant lesions at the time of initial examination.

## EPIDEMIOLOGICAL ASPECTS

The source of tuberculous infection at Pennhurst can roughly be divided into the two groups, extrinsic and intrinsic. Under extrinsic can be classed the infections brought into the institution by patients who are infected at time of

admission and those introduced by contact with visiting relatives and friends. Intrinsic, on the other hand, is used to designate cross-infections from infected inmates and employees.

Analysis of the 78 deaths from tuberculosis during the years 1932 to 1935 had shown that 15 per cent of the deaths had occurred one year or less after admission, suggesting that the disease had been present at the time of commitment. An opportunity for determining this was afforded on completion of the survey, for a routine of tuberculin-testing all new admissions and obtaining chest roentgenograms of the positive reactors had been instituted. During the years 1938 to 1939, a total of 281 new patients were admitted to the institution. Of these, 91, or 32.4 per cent reacted positively to the tuberculin test (0.1 mg. Old Tuberculin), which is in marked contrast to the 81.6 per cent positive reactors in the original survey group. Three or 1.1 per cent of the new admissions were found to have clinically significant lesions, a much lower incidence than the 4.4 percent noted in the survey. In the years following, the preliminary tuberculin testing was dispensed with and all new admissions were examined roentgenologically as a routine. From 1940 to 1946, a total of 1,359 new patients were admitted with 14, or 1.03 per cent, showing significant lesions. These figures show the value of routine roentgenologic examination on admission to weed out the infectious cases.

The findings presented above are in keeping with the type of patient admitted to Pennhurst and would tend to explain the high incidence of tuberculosis in the past. Most of the patient population is drawn from large cities where the incidence of tuberculosis in general is admittedly higher than in the rural districts. In Torrance State Hospital, where the patients are drawn from rural or country districts, the tuberculosis problem is not so great. Of 108 deaths in that institution, only 8, or 7.4 per cent were caused by tuberculosis, whereas at Pennhurst during the same year 28.4 per cent of the deaths resulted from tuberculosis.

No opportunity for screening the relatives or visitors was afforded, but it is certain that some infection was transmitted from them when it is recalled that a family history of tuberculosis was noted in 7.2 per cent of cases.

The major form of intrinsic infection is that resulting through cross-infection from infected inmates. The intimate association of patients in institutional life permits for greater exposure from unknown and unisolated infectious cases than would occur from such cases in the average community. The overcrowding, lack of suitable buildings, and inadequate personnel has tended to magnify this factor in recent years.

Plunkett (19) has amply demonstrated that every case of reinfection tuberculosis which develops during residence in an institution is usually associated with the presence of another infectious case in its immediate environment. On the other hand, inmates who are not in contact with open tuberculosis will not develop reinfection tuberculosis. These facts were borne out by the present survey. The high incidence of reinfection tuberculosis, both healed (3.8 per cent) and clinically significant (4.4 per cent), in the patients at the time of survey stands in contrast to the rate among new admissions (1.03 per cent) and



clearly demonstrates the tremendous rôle of intramural spread of the disease.

A potent source of intrinsic infection in any institution is the employee personnel. At Pennhurst, 5 cases of active tuberculosis have so far been detected in employees who had been actively in contact with patients.

#### FINDINGS SUBSEQUENT TO THE SURVEY

Despite the thorough study in 1938 and 1939, fairly heavy exposure has continued within the school, for a total of 48 new cases of active parenchymal tuberculosis and 8 cases of pleural effusion, presumably tuberculous, have been detected up to the end of 1946 in patients who were either tuberculin negative or who had had negative chest roentgenograms. This represents an incidence of 3.5 per cent in the original group after the then detected cases have been eliminated. This may in part be a result of exposure to open cases of tuberculosis prior to the completion of segregation. Similarly, 44 cases of active reinfection tuberculosis, 8 cases of pleural effusion, and 6 cases of active primary tuberculosis have been detected in the 1,640 new admissions from 1934 to 1946 who were negative on roentgenologic examination at time of admission. This represents a general incidence of 3.6 per cent in this group, or virtually the same incidence as in the old group.

This high incidence of tuberculosis is reflected in the death rate through the years. The percentage of total deaths caused by tuberculosis is presented in figure 1. It may be seen that after the survey was completed in 1939, a sharp decline occurred, undoubtedly a consequence of the fact that the active cases had been isolated and treated. Most of these patients, however, eventually succumbed to tuberculosis and the curve attained a new high in 1944 when more than 50 per cent of the deaths were from this cause.

The continued high death rate from tuberculosis was to be expected in view of the high incidence of new cases in the old and new groups of cases. The increased death rate in 1942 and 1944 parallels the greater incidence of active cases in these years. In some measure this can be attributed to the shortages incident to the war (material and personnel), and the probable admission of undetected active tuberculosis with subsequent cross-infection. Shortage of personnel also contributed to delay in clinical detection of active cases until they were in an advanced stage. Actually 47 per cent of the 92 cases detected after 1939 were in a far advanced state when the diagnosis was finally made.

The persistence of the high mortality rate after the survey can also be accounted for in part by the more accurate diagnosis of tuberculosis resulting from the more extensive use of roentgenologic examinations. In fact, it is most probable that the death rate was higher in the presurvey years than that officially recorded.

#### DIAGNOSIS OF TUBERCULOSIS IN THE MENTALLY DEFICIENT

It is common experience, amply corroborated by McCain (20) and Fellows (21), that, after the reinfection type of tuberculosis has produced lesions sufficiently large to be roentgenologically demonstrable, there frequently is a period

of two or three years before symptoms appear. Moreover, when symptoms do appear, more than three-fourths of the patients are either in the moderately advanced or far advanced stages.

The methods of diagnosis commonly applied to normal patients are fully applicable only in the higher grade mentally deficient. In these cases an adequate history can usually be obtained and any deviation from the normal easily recognized. But in the idiot and imbecile classes the problem is infinitely more difficult, due to the inability of the patient to coöperate. No subjective history can be given by these patients and the examiner must rely on unexplained loss of weight, loss of appetite, and fever unaccountable on some other basis, for the first indication that something is wrong. In this institution all patients are routinely weighed only once a month and frequently several months pass before the significance of weight loss is recognized. In the cases where cough or hemoptysis are present early, the chances of an early diagnosis are better but frequently these manifestations reflect the presence of advanced disease.

PER CENT OF TOTAL DEATHS DUE TO TUBERCULOSIS  
FROM 1932 TO 1946

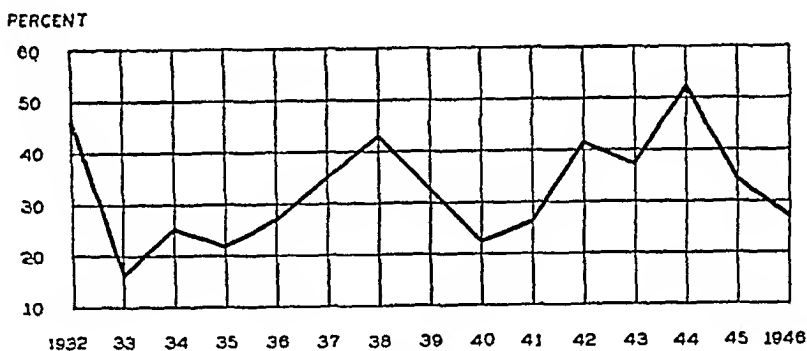


FIG. 1

Physical examination of the chest can be carried out in some measure as regards inspection and percussion, but palpation is less reliable and auscultation of very little value. It is difficult to get these patients to breathe properly and the use of the cough to produce râles is impossible. Many of the lower grade patients become afraid or agitated at time of examination which makes eliciting of abnormal signs difficult.

Routine laboratory studies can be done fairly easily, but sputum examinations are seldom possible in the low grade patients for they do not expectorate. However, passage of a tube into the stomach can be done fairly easily with a little patience; and examination of the gastric contents for tubercle bacilli can readily be carried out. In most of the cases of the present study, the bacteriologic diagnosis was established by this method.

Roentgenologic examination, though not as efficient as in the normal class is by far the most accurate and practical method available. By patient and intelligent handling of the patients, satisfactory films can be obtained in almost all

eases. Interpretation of these films, however, must allow for wide aberrations from the normal as regards technical factors and quality of the plates.

Review of the diagnosed cases since 1939 has readily emphasized the lack of correlation between lesions manifest on the roentgenogram and the symptoms and physical findings. In only 6 of the 92 cases of proven tuberculosis was the nature and extent of the disease predicted before the roentgenogram was obtained. It has been the experience of virtually all workers in this field that earlier detection of tuberculous lesions must depend on more frequent use of roentgenologic examinations.

#### TREATMENT OF TUBERCULOSIS IN THE MENTALLY DEFICIENT

Treatment of this type of case must of necessity be modified not only by the extent of involvement, but also by the degree of mental deficiency. As a rule, no therapy is applicable in the low grade other than isolation and general hygienic care. These patients are difficult to feed and keep clean and invariably show a rapid and progressive downhill course. Most of them can be kept in bed, but the agitated type constitute a great problem for they roam all over the ward contaminating themselves and other patients.

The use of collapse measures has only limited application in feeble-minded patients. In addition to the usual criteria for selection of suitable cases for collapse therapy the degree of mental deficiency must also be taken into consideration. In the present study, no attempt was made to give artificial pneumothorax except in those cases where a certain degree of coöperation could be expected. In general, the procedure has been effective in only 20 per cent of the cases in which it has been applied.

Other forms of collapse therapy have even more limited application. Internal pneumonolyses have been done successfully in 2 of the satisfactory pneumothorax cases. No case has been encountered in which thoracoplasty was considered advisable. Pneumoperitoneum has been applied in 5 cases with unsatisfactory results.

#### TUBERCULOSIS CONTROL MEASURES

The original survey and the subsequent studies have amply demonstrated the seriousness of the tuberculosis problem in institutions for the mentally deficient. To combat this adequately there must be strict adherence to definite policies designed to safeguard the health of both patient and worker alike. Segregation and adequate treatment of all inmates with active parenchymal infection must be effected, for most of these patients cannot be disciplined or taught hygiene. It is most desirable to have the infectious cases in a separate tuberculosis ward or building adjacent to the infirmary or hospital proper. In fact, in planning institutions it is essential that at least 5 per cent of the bed capacity be set aside for patients with tuberculosis.

Periodic reëxamination of all inmates, preferably on an annual basis, must be carried out. Patients should be examined clinically and, if there is the slightest suspicion of tuberculosis, a chest roentgenogram should be obtained. Sup-

posedly healed cases must be closely watched so that breakdown of lesions and progression will not be overlooked. These cases should be routinely examined roentgenologically every year, or more often if indicated.

All new admissions to the institution, whether patients or employees, should be properly examined and should have a routine roentgenogram of the chest. All definite and suspicious cases should be admitted to the tuberculosis ward for evaluation and disposition. Similarly, all discharged or paroled patients should be examined to prevent a case of active disease from entering into the community at large.

Not to be neglected should be improvement in the general hygienic condition of the buildings in which patients are housed. There should be less overcrowding and better ventilation. This can only be accomplished by expanded building programs, either by remodeling old buildings or erecting new ones. In any event, smaller dormitories should be planned to provide less intimate contact between patients.

In view of the current enthusiasm for BCG vaccination, its use must be seriously considered in this type of patient. If it can be depended upon to produce any immunity at all, its value should be immense in institutions where the infection rate is so high. It would seem desirable to give all old patients and all new admissions who are tuberculin negative the benefit of this vaccination.

#### SUMMARY AND CONCLUSIONS

1. The clinical aspects of tuberculosis in a 2,400 bed state institution for the feeble-minded have been discussed.

2. A total of 1,733 patients were intensively studied. A positive tuberculin test (0.1 mg. Old Tuberculin) was found in 1,415, or 81.6 per cent. The rate of infection was in inverse ratio to the mental age, and directly proportional to the chronological age.

3. Of the positive reactors, 142, or 8.2 per cent, of the total group surveyed were found to have lesions characteristic of the reinfection type of pulmonary tuberculosis. Of these, 77, or 4.4 per cent, were classed as clinically significant and 65, or 3.8 per cent, as healed.

4. The rate of tuberculous disease is in direct proportion to the degree of mental deficiency, being highest in the idiot class. The incidence in the two higher grades (moron and borderline) essentially parallels that found in the extramural population at large.

5. Reexamination of the diagnosed cases seven years after the original survey shows that 50.6 per cent of the clinically significant cases are now dead. In the healed category, 17.3 per cent have died from tuberculosis and an additional 17.3 per cent have shown reactivation of their lesions.

6. Routine roentgenologic examination of 1,640 admissions since the survey shows an incidence of 1.03 per cent clinically significant lesions at time of admission. Of the remaining, 3.6 per cent subsequently developed either active reinfection type lesions, a pleural effusion, or active primary tuberculosis.

7. Three and five-tenths per cent of the original survey group, who were either

tuberculin negative or who had normal chest roentgenograms in 1939, subsequently developed an active reinfection type of tuberculosis.

8. Five cases of active tuberculosis have been detected in employees actively in contact with patients. Employees in this type of institution are more exposed to tuberculosis and constitute a problem for industrial compensation.

9. The use of BCG vaccination as a prophylactic measure should be considered in this type of institution where the infection rate is so high.

#### SUMARIO Y CONCLUSIONES

##### *Tuberculosis en los Débiles Mentales*

1. Reséñanse las fases clínicas de la tuberculosis en un establecimiento estatal de 2,400 camas para débiles mentales.

2. En total, se estudió intensamente a 1,733 enfermos. En 1,415 (81.6 por ciento) la reacción a la tuberculina (0.1 mg. de T. A.) resultó positiva. El índice de infección se mostró en razón inversa a la edad mental y en proporción directa a la edad cronológica.

3. De los reactores positivos, 142, o sea 8.2 por ciento del grupo total estudiado, revelaron características lesiones del tipo reinfección de la tuberculosis pulmonar. De éstas, 77 (4.4 por ciento) fueron clasificadas como clínicamente importantes y 65 (3.8 por ciento) como cicatrizadas.

4. El coeficiente de enfermedad tuberculosa se halla en proporción directa al grado de deficiencia mental, alcanzando el máximo en la casilla de los idiotas. La incidencia en los dos grados más altos (morón y limítrofe) más o menos paralela la descubierta en la población extramural en conjunto.

5. La reexaminación de los casos diagnosticados a los siete años de la encuesta primitiva revela que 50.6 por ciento de los casos clínicamente importantes ya han muerto. En el grupo de los cicatrizados, 17.3 por ciento han muerto de tuberculosis y otro 17.3 por ciento han mostrado reactivación de sus lesiones.

6. El habitual examen radiológico de 1,640 enfermos admitidos desde la encuesta revela una incidencia de 1.03 por ciento de lesiones clínicamente importantes en la fecha del ingreso. Del resto, 3.6 por ciento manifestaron después, bien lesiones activas de tipo reinfección, derrame pleural o tuberculosis primaria activa.

7. Un 3.5 por ciento del grupo estudiado primitivamente, que habían sido negativos a la tuberculina o los rayos X en 1939, manifestaron después una tuberculosis activa de tipo reinfección.

8. Entre los empleados en contacto frecuente con los enfermos se han descubierto cinco casos de tuberculosis activa. El personal de los establecimientos de este género se halla más expuesto a la tuberculosis y plantea un problema en cuando a indemnización profesional.

9. En estas instituciones en las que el coeficiente de infección es tan alto, debe considerarse al empleo de la vacunación BCG como medida profiláctica.

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## AMERICAN TRUDEAU SOCIETY

### *Report of the California Trudeau Society*

By Harold Guyon Trimble, M.D.

The annual meeting of the California Trudeau Society was held at Long Beach, March 31, 1948, to April 3, 1948. This was the 1948 annual meeting of the California Tuberculosis and Health Association, the Clinical Section being under the California Trudeau Society.

The following program was presented:

Thursday, April 1

9 A.M.

Thomas B. Wiper, M.D., Chairman

*Tuberculosis of the Skin*—Frederick G. Novy, M.D., Oakland: Doctor Novy gave the various descriptive terms that are used by dermatologists and said he felt there was need of a good clinical classification. The lesions are mainly divided into localized forms and hematogenous forms. Doctor Novy described the treatment of lupis vulgaris with large doses of Vitamin D<sub>2</sub> as spectacular. He believes that this treatment is also of value in sarcoidosis. Streptomycin is excellent for direct infections, such as those on butchers' hands.

*Tuberculosis of the Genito-Urinary Tract*—Thomas Conroy, M.D., Palo Alto. Renal tuberculosis is always hematogenous. When destruction occurs, these lesions do not heal. Surgery is a phase in the handling of a generalized disease. The primary source is pulmonary in 82 per cent of the cases. Excretory pyelograms are of value when positive, but retrogrades are usually necessary. Specimens of urine from each kidney must be obtained for study. Retrograde pyelograms in this situation are not dangerous. Some cases of renal tuberculosis have been reported to heal, but these are very rare. Nephrectomy is unchallenged as the treatment indicated, even in some cases known to be bilateral, if one kidney is very much the worse. Streptomycin is useful in handling these cases, particularly for the complications. Ultraviolet is helpful. As far as streptomycin is concerned, there is as yet no extensive series available for evaluation. Surgery of a tuberculous kidney should be done under the "protection" of streptomycin. The pyelographic changes do not respond to this drug and after stopping streptomycin, the disease in the kidney usually progresses.

*Tuberculosis of the Eye*—Alexander Ray Irvine, Jr., M.D., Los Angeles: Dr. Irvine stated that some alleged instances of ocular tuberculosis are definite tuberculosis infections, while others are less easily proven. Tuberculin in large doses is dangerous. It may be of some help in small doses but one must use extreme care or blindness may ensue. Gold salts have no value. Non-specific proteins are widely used. Sulfones have been of some help in rabbits. Beta radiation may be helpful in occasional patients.

*Tuberculosis of the Bone and Joint*—Donald E. King, M.D., San Francisco: Doctor King presented an interesting group of orthopedic cases illustrated by a series of photographs and lantern slides. Some of these cases were misdiagnosed at first. With regard to ankles and knees, Doctor King recommends ankylosis, removing the diseased tissue at surgery, but not extirpating the entire joint if possible. Spinal fusion is one of the best operations but here the diseased tissue cannot be removed. It is very urgent not to operate while the lesions are showing acute manifestations.

Robert S. Huntington, M.D., of Los Angeles, discussed the pathology of tuberculosis of the skin, genito-urinary tract, eyes, bone, and joints, the clinical manifestations of which had been presented in the preceding group of papers.

2:00 P.M.

Clinical Section, Cabot Brown, M.D., Chairman

*Bronchogenic Cancer, Diagnosis by Cytological Studies of Sputum and Bronchial Secretions*—presented by Mortimer Benioff, M.D., with Seymour Farber, M.D., John Frost, M.D., Miss Miriam Dusehkin, all of San Francisco: Doctor Benioff stated that cancer of the lung is almost always bronchogenic in origin and that the cells will exfoliate and follow the normal bronchial drainage. They can be detected in 80 per cent of all cases. The first work was reported by Welch in 1840. In 1887, cancer particles in the sputum were reported from unstained sputum. In diagnosing lung tumors, more adequate methods are needed. South American reports on sections of bronchial secretions vary from 65 to 100 per cent accurate diagnoses. The method is slow and expensive and requires almost serial sections. Some method of wet fixation is required. Papanicolaou has worked since 1913 on vaginal smears, and reported some of his cases in 1923. It took until 1943 to stimulate interest in pulmonary secretions. Herbert and Clerf of Philadelphia applied the technique to bronchial secretions with satisfaction.

In the present study, normal cellular constituents were first studied. The investigators then studied freshly excised and autopsy material from which surface smears were obtained. Diagnostic of malignancy are: first, the aggregate of cells; second, variation of size and shape of nuclei; third, the crowding of the cells; fourthly, large nuclei with little cytoplasm; fifthly, irregular nuclei.

Squamous cell and adenomatous types are easy to diagnose. The small or oat cell types are difficult to identify from cells normally present in the sputum. Routine study of 200 autopsy cases of carcinoma of the lung were reviewed and only 101 were diagnosed before death. Other diseases may be present. Dr. Benioff and his associates have observed in this series 17 cases of coexisting pulmonary tuberculosis and carcinoma.

Out of 1,176 specimens from 321 patients, there were 62 specimens positive for malignant cells, 38 cases proved to be malignant by this method.

There was one case of a false positive that had atypical macrophages present. Examination of sputum is of definite value, whether or not it is obtained through bronchoscopy. Fresh sputum is spread on a black background, suitable pieces smeared and fixed immediately. No training is required to make this smear, but skill and judgment is required for diagnosis. This is a useful procedure but depends upon a well trained pathologist who knows tissue cells.

*Pleural-Pulmonary Amebiasis*—A. C. Daniels, M.D., W. L. Rogers, M.D., San Francisco: These investigators report a high percentage of infection in the United States population by amoeba histolytica in the intestinal tract. It is uncommon to spread except to the liver. The infection may go from there to the pleura and then to the lung. In treatment, surgical drainage had a 50 per cent mortality, surgical drainage plus emetine 15 per cent mortality, emetine alone without surgery 5 per cent mortality. There was a prompt resolution of the pulmonary lesions observed with emetine treatment. The author reviewed the literature and reported 6 personally observed cases of pulmonary-pleural amoebic disease.

*Therapeutic Pneumoperitoneum in the Treatment of Pulmonary Tuberculosis* was presented by Harold Guyon Trimble, M.D., and J. Lloyd Eaton, M.D., of Oakland. This report represents a study of 407 consecutive cases of tuberculosis treated with pneumoperitoneum from 1934 to 1946. The literature was reviewed, the technique was discussed briefly and several cases were presented which illustrated the type of disease most suitable for treatment and the results obtained. The complications were analyzed. Significant complications were observed in six per cent of the series. The clinical status of the patients at the end of the study was reviewed.

Including all of the patients with cavities totaling not more than 8 cm. in diameter, there was a total of 171 such patients. Ninety-six, or 56 per cent, became arrested and



another 27, or 16 per cent, were definitely improved. On the other hand, of the 52 patients with cavities larger than 8 cm. only 10, or 19 per cent, became arrested, with an additional 13 patients definitely improved. This illustrates the fact that the best results are found with the single cavities, but the results are good in all cavities whose total diameter does not exceed 8 cm. At this point there is a sharp decline in the expectancy of arrest.

Analysis of the position of the cavity, whether apical, mid-lung, or basal, showed that the position in the lung had but little bearing on the results which may be expected from pneumoperitoneum therapy. The percentages of each group, those arrested, improved, unsatisfactory and dead, as compared with the three separate locations of the cavity, are extremely close but slightly more favorable results were observed in the treatment of the basal cavities.

The authors feel that building on a foundation of bed-rest plus a short period of institutional care for educational purposes, therapeutic pneumoperitoneum is an excellent procedure. They conclude that the purpose of pneumoperitoneum is to achieve an adequate mechanical rise of the diaphragm, thus reducing the pulmonary volume and limiting the motion of the diaphragm with ordinary respiration. To be maintained, large weekly refills are necessary, guided by fluoroscopy.

Manometric readings are of minimal value as a guide to the extent of the collapse. Phrenic nerve operations are usually not necessary and are used only for specific and definite indications, which are few.

Adequate pneumoperitoneum is a valuable collapse procedure in the treatment of pulmonary tuberculosis. Their immediate and longtime results amply confirm this. The period of complete bed-rest is much shortened, complications are not excessive, and are rarely serious. Their indications for pneumoperitoneum therapy have been greatly widened because of: (1) the good results obtained; (2) as compared with bed-rest alone, the shortened period of complete bed-rest with the resultant economic saving to the patient, the low exacerbation and recurrence rate, the more rapid conversion of sputum, the possibility of changing to a more radical collapse procedure should the need arise; (3) as compared with pneumothorax, the fact that pneumoperitoneum can be initiated in nearly all patients, the fact that it is a completely reversible procedure and can be stopped at any time without danger of a non-expansile lung or pleural complications, the possibility of reinitiating it should the need occur, and the relative lack of complications.

*Management of Tuberculosis Effusions and Empyemata*—Reginald H. Smart, M.D., Stanford S. Kroopf, M.D., Los Angeles: These are defined as any serous effusion having a tuberculosis etiology. The authors believe they are always associated with some parenchymal disease. This may be shown by the frequency of positive gastric lavage when the roentgenogram is negative. Many may be present because of inadequate pneumothorax which has been continued too long. Management includes bed-rest under sanatorium conditions, removal of fluid, and the introduction of air. The underlying parenchymal disease must be controlled. Streptomycin is not effective in the local control of fluid due to the unfavorable pH of the fluid. Attempts to sterilize the fluid have been largely ineffective and usually cause marked pleural thickening with non-expansile lungs. Oleothorax is not satisfactory when the cases are followed for a long enough period of time. The use of promin intrapleurally may be helpful. Empyema cavities must be obliterated by phrenic paralyzes or thoracoplasties. Pleural decortication is possible if the underlying pathological lesion has been controlled. The authors use promin 5 per cent in distilled water (100 cc.) intrapleurally three times each week. Purulent fluid rapidly becomes serous and many entirely disappear. Thirteen cases are reported. The intrapleural use of sulphonamides is not advisable because of the resultant marked pleural thickening.

In mixed infection, the authors advise the use of penicillin intrapleurally and penicillin plus sulphonamides systemically. Tyrothricin intrapleurally is not effective. Pleurotomy flap drainage has not been helpful in the experience of these authors.

*Bronchiectasis Masked by Pleural Effusion*—Allen Lilienthal, M.D., San Francisco: The

speaker presented four cases showing the masking by pleural effusion of definite bronchiectasis. This complicates the making of an accurate diagnosis. If there is history of bouts of pneumonitis and cough and sputum, he advises that the sputum be measured daily and estimated as to its character. The author suggests that bronchoscopy and bronchograms should be used more frequently in studying patients with pleural effusions.

Friday, April 2

9:00 A.M.

Joint Session: Public Health Section and California Trudeau Society

Mr. John W. Popovich, Chairman

Louis E. Martin, M.D., the retiring president of the California Tuberculosis and Health Association reviewed the accomplishments of the Association for the past year.

*Treatment of Clinical Tuberculosis by Streptomycin*—Arthur M. Walker, M.D., of Washington, D.C.: Doctor Walker reviewed 1,775 Veterans Bureau cases from June 1946 to October 1947. The development of *in vivo* resistance to streptomycin by the tubercle bacillus during treatment was one of the great bars to its more effective use. The present thought was that a few initially resistant organisms continue to reproduce and become dominant. Complete resistance develops around forty-two days. Streptomycin is useful as a prophylactic in thoracic surgery when administered four days before and fourteen days after surgery. Streptomycin is probably not necessary in thoracoplasty, but in pulmonary excision it is very helpful.

Doctor Walker analyzed 100 cases of acute miliary and meningeal tuberculosis. Sixty died and 40 were alive in October 1947.

The Veterans Administration series of cases of orthopedic tuberculosis was analyzed from August 1946 to February 1948. There were 94 patients with 112 lesions: 58 spine, 37 extremities, and 17 of other bones. Seventy per cent of the series showed some improvement but this was not striking.

Forty-nine cases of genito-urinary tuberculosis were treated from October 1946 to October 1947. Urine cultures were negative for tubercle bacilli in 69.4 per cent of the group. The dose of streptomycin used was 1.8 or 2.0 grams intramuscularly for one hundred and twenty days. There was no demonstrable effect on the kidney lesions themselves.

Doctor Walker reported the results observed in pulmonary lesions in 223 patients at 1.8 grams daily dose. Improvement in weight, appetite, cough and sputum was prompt, and within two weeks there was reversal of the trend of the disease in 85 per cent of these patients. In 182 patients with cavities, 25 per cent closed. Thirty per cent of 195 cases relapsed after treatment. Tongue, tonsil, and pharyngeal lesions all do remarkably well.

Tuberculous enteritis, 33 cases: Definite general improvement after only the intramuscular use of streptomycin was noted in 33 cases.

Twenty-eight cases of tuberculous peritonitis (26 proved) were treated, with excellent results. Two of these cases had laparotomy after treatment and a normal peritoneum was discovered on biopsy.

Sixty tuberculous sinuses in 12 patients were treated and 59 were healed within one to twenty weeks.

Tracheobronchial tuberculosis, 50 cases: Sixty-two per cent of 50 cases of tracheobronchial tuberculosis were healed, 32 per cent improved and 6 per cent were not improved, on intramuscular streptomycin therapy for thirty to one hundred and twenty days.

*The Place of the Practising Physician in the Field of Preventive Medicine* was presented by Wilson G. Smillie, M.D., of Cornell University Medical College, New York City. This was a masterly discussion developing the theme that the primary concern is not with the disease, but with a sick individual.

2:00 P.M.

Clinical Section, Howard W. Bosworth, M.D., Chairman

*Tuberculosis in Childhood*—Lloyd B. Diekey, M.D., San Francisco: The author stated he had confidence in intradermal tuberculin tests, but not in patch tests. Contacts with a positive reaction should be periodically examined. The differential diagnosis between tuberculosis and other conditions is important. The principal source of confusion is usually only the roentgenographic findings and a careful history and adequate study will usually define the pathological problem. The speaker stated that in children careful attention should be paid to diet because of the growth factor. He felt that BCG needed adequately controlled study for evaluation and definitely should not be substituted for removal of contacts. The general feeling in pediatric circles is somewhat different from that apparently being reached among plithisiologists. Pediatricians would receive the widespread use of BCG very reluctantly at the present time.

*Endogenous versus Exogenous Reinfection in Tuberculosis*—F. M. Pottenger, M.D., of Monrovia: The speaker discussed the question of how dependable was the immunity produced by a first infection. One must assume that subclavicular lesions are the result of localized metastases from preëxisting foci. He cited Papworth and Davos' experiences as examples. Doctor Pottenger advocated the use of BCG to stimulate the immunity mechanism.

A Round Table Conference was held on the use of streptomycin in the treatment of tuberculosis, Richard H. Meade, Jr., M.D., Grand Rapids, Michigan, Arthur M. Walker, M.D., Washington, D. C., Emil Bogen, M.D., Olive View, and Howard Bosworth, M.D., Los Angeles, participating.

8:00 P.M.

Clinical Roentgenographic and Pathological Conference

John L. Gompertz, M.D., Chairman

The panel consisted of Reginald H. Smart, M.D., Los Angeles; David Dugan, M.D., Oakland; Wilbur Bailey, M.D., Los Angeles; Chesley Bush, M.D., Livermore; Rufus A. Schneiders, M.D., San Diego. A group of interesting cases was presented and discussed.

Saturday, April 3

9:00 A.M.

Clinical Section, John C. Jones, M.D., Chairman

Surgical Symposium

*Pulmonary Resection: A Treatment for Pulmonary Tuberculosis*—Richard H. Mead, Jr., M.D., Grand Rapids, Michigan, presented a survey of the various groups of cases reported and brought them up to date by personal correspondence.

*Anesthesia in Thoracic Surgery*—Marshall L. Skaggs, M.D., San Francisco: The marked improvements in anesthesia with reference to lung surgery were critically reviewed.

*Surgical Aspects of Pulmonary Calcification*—Alfred Goldman, M.D., Beverly Hills, presented a group of cases of large pulmonary calcification removed surgically in which the calcification had been largely responsible for the symptoms with resultant benefit to the patient.

*Surgery of the Heart and Great Vessels*—H. Brodie Stephens, M.D., San Francisco: The speaker reviewed the anatomy, surgical approach, and results of treatment in a group of congenital cardiac abnormalities.

# THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

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**Spontaneous Bilateral Pneumothorax.**—About 100 cases of spontaneous bilateral pneumothorax are to be found in the literature, a number of them reported from Argentina in the last few years. While the condition is not considered serious, many of the cases take a turn for the worse, and Oeschli and Miles place the case death rate at 55.7 per cent. In the case reported here, at Rio de Janeiro, bilateral pleuroscopy was followed by intrapleural injection of dextrose solution, with successful results. In both lungs many air bubbles were present. An X-ray taken two years afterwards showed normal pleuro-pulmonary fields. —*Pneumotórax espontâneo bilateral simultâneo: Pleuroscopia e pleurodese bilaterais, J. M. Castello Branco, Clín. tisiol., (Rio de Janeiro), April-June, 1947, 2: 213.*—(A. A. Moll)

**Emphysema and Medicinal Aerosols.**—The author reports his experience in the treatment of emphysematous patients by the administration of aerosols having the property of dilating the bronchial passages, presumably by relieving spasm of the bronchopulmonary musculature. A previous communication was concerned with their use in asthma with favorable results. In this study he treated 21 patients with aleudrine alone and 18 patients with a combination of aleudrine, idrianol and novocaine. Aleudrine is a very active isopropyl-adrenaline, several times more active than adrenalin. It is said to relieve dyspnea when given orally in the form of compressed tablets, but is much more effective and produces more lasting results if used as an aerosol according to the author's method and with his special

apparatus. At first the treatments are given daily. Each series of inhalations consisted of ten very deep inspirations of the aerosol followed by a period of breath suspension and then by rapid and deep expirations. Three such series are prescribed daily for a month. Then they are repeated three times a week for two months, twice a week for three months, and once a week for four months. The concentration of aleudrine used was three parts per thousand. In evaluating the results, patients who reported prolonged absence of dyspnea, though admitting occasional slight difficulty in breathing which soon disappeared spontaneously, were classed as 90 per cent improved; those who continued to have slight dyspnea, especially after a full meal, easily relieved by mild sedatives, were considered to be 75 per cent improved; those who continued to have dyspnea, especially on effort, which however was much less severe and did not prevent their continuance of their usual activities, were classed as 50 per cent improved; those who showed some improvement but only after prolonged treatment were called 25 per cent improved. Five of the 21 patients treated by aleudrine alone were 75 per cent improved, 8 were 50 per cent improved, 3 were 25 per cent improved, and in 5 the treatment failed entirely. In the second series of 18 patients for whom a mixture of aleudrine, three parts per thousand, idrianol 2 per cent, and novocaine 2 per cent was used, 3 patients were 90 per cent improved, 8 were 75 per cent improved, and 7 were 50 per cent improved. There were no failures. The author attributes these improvements to the increase of oxygen in the arterial system and in the tissues

resulting from dilatation of the air passages, and also to better oxygenation of the heart muscle itself.—*Emphysème pulmonaire et aérosols médicamenteux*, R. Charlier, *Le Poumon*, May-June, 1947, 3: 199.—(A. T. Laird)

**Sarcoidosis.**—Twenty-eight cases of sarcoidosis, admitted to an Army general hospital between July 1, 1942 and April 1, 1946, are reviewed. Fifteen of the patients were Negroes. The symptoms were: cough in 9 cases, hemoptysis in 2, dyspnea in 11, chest pain in 6, weight loss in 6. Enlargement of peripheral lymph nodes was seen in 26 cases. The eyes were involved in 11 cases. Tuberculin tests were done in 25 patients: there was no reaction in 21, a doubtful reaction in 2, and in 2 cases there was a weakly positive reaction. The total blood protein was elevated in 19 and the globulin was elevated in 23 of 27 patients in whom such studies were done. Blood calcium was determined in 16 cases; it was increased in 10. The alkaline phosphatase was elevated in 5 of 14 patients. Leukopenia was found in 7 patients, eosinophilia in 7. Roentgenological studies revealed enlargement of the paratracheal lymph nodes in all patients, enlargement of the peribronchial lymph nodes in 25, pulmonary parenchymal involvement in 15, pleural effusion in 2, pericardial effusion in one, and osseous changes in the hands in 6. The lymph nodes remained discrete, being later replaced by fibrous tissue. One patient died because of respiratory embarrassment. In 2 cases roentgen treatment was given to the enlarged lymph nodes, without any effect.—*Sarcoidosis: A Clinical and Roentgenological Study of Twenty-eight Proved Cases*, J. J. McCort, R. H. Wood, J. B. Hamilton & D. E. Ehrlich, *Arch. Int. Med.*, September, 1947, 80: 293.—(G. C. Leiner)

**Carcinoma of the Lung.**—Over a period of twelve years 412 patients with cancer of the lung were seen at the Charity Hospital and at the Ochsner Clinic, New Orleans. Of these, 246 underwent surgical exploration and 147

were subjected to primary pulmonary resection. There is a definite increase in the incidence of this disease primarily among white patients, with little or no change among Negroes. Approximately 90 per cent of the patients were in the fifth, sixth and seventh decades of life; 86.4 per cent were men. The right lung was involved in 59 per cent of the 147 cases of resection. A roentgenographic diagnosis of bronchogenic carcinoma was made in 82.3 per cent of the 147 cases; bronchiographic examination was performed in 47 per cent. The latter method is particularly valuable when the lesion is located in the periphery of the lung or in an upper lobe. Bronchoscopy was performed in 125 of the 147 resected cases; in 61 instances a positive diagnosis was made by this method. Cytologic examination of the sputum or bronchial secretions will prove of increasing importance as a diagnostic procedure. Aspiration biopsy should not be used since it creates the danger of implantation of tumor cells in the needle tract. In 66 per cent of the 246 cases in which an exploratory operation was performed, a positive diagnosis was established prior to operation. Involvement of the phrenic and recurrent laryngeal nerves was not considered a contraindication to exploration. The hospital mortality before and after 1942 was 46.4 per cent and 19.3 per cent, respectively. Empyema developed in 12.2 per cent of the 147 cases. The average hospital stay was 32.3 days before 1942 and 13.5 days after 1942. Of the patients operated on five years ago or more, 23 per cent are still alive.—*Primary Cancer of the Lung*, A. Ochsner, M. DeBakey & J. L. Dixon, *J. A. M. A.*, October 11, 1947, 135: 321.—(H. Abeles)

**Planigraphy in Lung Cancer.**—Planigraphy (body section roentgenography) is of value as a supplementary method in the diagnosis of carcinoma of the lung. Its accuracy compares favorably with other X-ray methods of diagnosis. Of 47 cases examined by planigraphy, diagnostic failures were noted in only 5 instances.—*Planigraphy in the Diagnosis*

of Bronchogenic Carcinoma, L. G. Rigler & T. B. Merner, *Am. J. Roentgenol.*, September, 1947, 58: 267.—(J. E. Farber)

**Apical Form of Bronchogenic Carcinoma.**—There are four stages in the clinical evolution of bronchogenic carcinoma situated in the apex: (1) The initial stage, with an apical X-ray shadow impossible to distinguish from apical pleurisy. Diagnosis is almost never made in this stage. (2) The stage of extrapulmonary invasion. There are pains in the shoulder and in the medial aspect of the homolateral arm. There may be symptoms of disturbance of the sympathetic system. (3) The stage of clinical characterization. In addition to the above there may be a lower brachial paralysis, Horner's syndrome and other sympathetic disturbances, phrenic nerve paralysis, recurrent nerve paralysis or, in left sided tumors, anginal symptoms. Masses may be present in the supraclavicular region and in the supra- and subscapular areas and there may be X-ray evidence of costal and vertebral osteolysis. (4) The fourth stage is always characterized, barring death from intercurrent illness, by the signs and symptoms of spinal cord compression with paraplegia. These clinical stages correspond pathologically to the extensions of the bronchogenic tumor, first within the lung itself, and later to invade adjacent neural and bony structures.—*La forma apical del cáncer bronco-pulmonar*, N. Romano & R. Eyherabide, *Rev. de tuberc. de Peru*, January-June, 1947, 24: 965.—(F. Percz-Pina)

**Giant Mediastinal Fibrolipoma.**—A large mediastinal fibrolipoma in a man 46 years old caused but few symptoms at first and was diagnosed as a benign intrathoracic growth. Suddenly a picture of extreme collapse developed through the intrapleural rupture of a superficial vessel of the tumor. This unusual complication and the diagnostic problems it raised even while operating make the case interesting. The postoperative course was favorable after a fibrolipoma weighing 2,400 g. (over 5 pounds) was removed. Most

of the cases reported in the literature are necropsy findings. Complications are uncommon and in most of the few cases operated the neoplasm weighed less than 500 g. However, Watson and Urban in 1944 reported a case operated successfully in which the growth weighed 3,100 g.—*Fibrolipoma mediastinal gigante: Hemolórax por rotura vascular*, G. Pollitzer & O. A. Vaccarezza, *An. Cdted. de pat. y clín. tuberc.*, June, 1946, 8: 145.—(A. A. Moll)

**Occupational Lung Disease.**—The literature of diseases of the lung caused by occupational dust other than silica is reviewed. Exposure to metallic dusts such as manganese, beryllium, vanadium and osmium causes chemical pneumonitis. A sarcoid-like syndrome may develop long after exposure to beryllium. Moldy vegetable matter such as hay, corn, bagasse and cotton, gives rise to acute bronchiolitis, but there is no conclusive evidence to support the theory that this is the result of a fungus infection. Complex salts of platinum give rise to a form of asthma. The incidence of carcinoma of the lung is abnormally high in persons exposed to arsenic dust. Metals according to atomic weight are opaque to X-rays and dusts such as ferric oxide and barium give rise to radiographic shadows called siderosis and baritosis, respectively. Silver is deposited in the elastic layer of arteries of workers exposed to its dusts. The silicates, particularly china clay, talc, mica, sillimanite and asbestos, give rise to various kinds of fibrosis in the lung though not to a nodular fibrosis like that caused by quartz and silica. Graphite appears to be harmless.—*Occupational Lung Disease*, K. M. A. Perry, *Thorax*, June, 1947, 2: 91.—(A. G. Cohen)

**Benign Pneumoconiosis.**—Three men employed as oxyacetylene steel cutters for seven to twenty-four years were found on roentgenological examination to have discrete nodulation or stippling of the lung fields. These findings, similar to those described for electric arc welding, include: (1) discrete and

rather sharply defined rounded densities of more or less uniform size and equal distribution in both lungs, (2) no tendency to confluence of the shadows, (3) hilum shadows always smaller than would be expected with silicosis of this degree (except during infections). None of the cutters has associated progressive tuberculosis which is further evidence of primary siderosis with little or no silicosis. In these patients there was no measurable impairment of lung function. Careful postmortem studies of cases of this type may some day show that all that is nodular by roentgen-ray examination is by no means always silicosis.—*Benign Pneumoconiosis Due to Metal Fumes and Dusts*, O. A. Sander, *Am. J. Roentgenol.*, September, 1947, 58: 277.—(J. E. Farber)

**Hemorrhage in Aberrant Lung Tissue.**—A case is reported of death as a result of a sudden internal hemorrhage. At necropsy the left pleural cavity was full of blood. A small tumor was found which was posterior and slightly to the left of the heart, attached to the mediastinum by a short narrow pedicle. A ruptured aneurysm surrounded by blood clot was found on the surface of the tumor. The lungs were normal. Sections of the tumor revealed collapsed lung tissue with persistence of numerous bronchioles and blood vessels. The picture was that of long-standing bronchiectasis. The case was therefore one of hemorrhage into an aberrant segment of lung tissue.—*Fatal Hemorrhage in Aberrant Lung Tissue*, F. D. Hart & A. C. Jones, *Lancet*, November 15, 1947, 2: 722.—(A. G. Cohen)

**Congenital Funnel Chest.**—The hereditary character of funnel chest has been pointed out previously. The author reports a group of 6 cases in three generations of one family. No other abnormalities were apparent. It is believed that the condition is inherited as a dominant character.—*Congenital Funnel Chest*, H. S. K. Sainsbury, *Lancet*, October 25, 1947, 2: 615.—(A. G. Cohen)

**Gastric Cysts.**—A case of successful removal of a large intrathoracic cyst in a 14-year-old girl is reported. The literature is reviewed.—*Intrathoracic Gastric Cysts*, E. W. Daris & D. Salkin, *J. A. M. A.*, September 27, 1947, 135: 218.—(H. Ables)

**Post - tracheotomy Complications.**—The clinical courses of all children having a tracheotomy during the four and one half years preceding May, 1946 were carefully observed at the St. Louis Children's and St. Louis City Hospitals. Previous observations had led to the belief that mediastinal emphysema, sometimes followed by pneumothorax, was the result of forced inspiration in the presence of an inadequate airway and an incision in the neck. It was decided to employ preoperative bronchoscopy whenever possible to decrease the hazard. Experiments on dogs showed that following tracheotomy and upper respiratory obstruction, air or dye or iodized oil was often found to be aspirated into the mediastinal tissue spaces, and even the pleural space. One hundred and twenty patients, all under the age of 10 years, had a tracheotomy for various acute inflammatory and mechanical obstructive indications. Dyspnea often persisted after the procedure, due to lower respiratory obstruction. Seventy-four cases were examined by lateral chest films, and 25 per cent of the cases were said to have mediastinal emphysema. Eighty-two cases were examined by an AP chest film, and 10 per cent had a pneumothorax. The advisability of preoperative clearance of the airway by bronchoscopy or aspiration has been shown by clinical data; the bronchoscope may even be indwelling at the time of operation. About 40 per cent were bronchoscoped before operation; the incidence of mediastinal emphysema was 70 per cent greater in those not bronchoscoped, and pneumothorax was 8 times as common (these figures are statistically significant). The frequent occurrence of the two complications indicates their importance in differential diagnosis during care of tracheotomized patients. Diagnosis requires careful physical examination and use

of the X-ray. Treatment consists of oxygen, a clear airway, and judicious aspiration of air.—*Further Observations on Post-Tracheotomy Mediastinal Emphysema and Pneumothorax*, G. B. Forbes, G. Salmon & J. C. Herweg, *J. Pediat.*, August, 1947, 31: 172.—(W. H. Oatway, Jr.)

**Case-Finding in Reykjavik.**—Legislation, efficiently organized Health Center work and the interest and co-operation of the public made possible, in the first four months of 1945, a tuberculosis case finding survey in Reykjavik, Iceland, in which 99.32 per cent of the entire population of nearly 46,000 persons was examined. Children from 1 to 13 years of age were tuberculin-tested by the Vollmer patch method while pupils between ages 13 and 20 were given the Mantoux test with P.P.D. Infants under 1 year were not tested. All positive reactors were roentgenographed. The remainder of the population was x-rayed and those with evidence of tuberculosis were given tuberculin tests. A group of 522 persons (1.17 per cent) consisting of invalids and the aged received only physical and sputum examinations. Tuberculous infection as revealed by tuberculin tests performed on 11,605 children and adolescents showed a slight increase up to the age of 12 when 12.4 per cent of the boys and 15.7 per cent of the girls were positive, and a more marked increase at 14 with 19.5 per cent of the boys and 18.1 per cent of the girls infected. At the age of 19, 44.2 per cent of the males and 45.2 per cent of the females reacted positively. There were found 808 cases with tuberculous lesions in the lungs previously unknown to the Health Center. These included 71 (1.6 per mille) cases of active tuberculosis, 75 (1.7 per mille) cases of indeterminate activity, the overwhelming majority of which most probably represented healed but not exclusively fibrotic or calcified lesions, and 622 (15.2 per mille) instances of fibrotic and calcified changes. 56.3 per cent of the active cases revealed positive bacillary findings. 60.3 per cent of the new active cases were in the age group 15-30 years and 8.4 per cent were above 60 years. 68 per cent

in the indeterminate group were 20 to 40 years of age, 6.7 per cent 60 or older. The number of fibrotic or calcified cases increased rapidly with age, culminating between 60 and 70 years. A comparison of the results of this survey with that of the ordinary work of the Health Center shows that 18.8 per cent of all active cases and 44.5 per cent of the indeterminate and fibrotic or calcified cases known to the Center in November 1945 were found through the survey, and that 63 per cent of all cases in the age group 50 and over and 85 per cent at and after the age of 70 had been unknown before. Therefore, if it is impossible to examine the whole population of a district, the age groups 15 to 30 and over 60 years should be preferred. By combining the previously known cases with those detected by the survey the prevalence of the population of Reykjavik is determined and analysed as to classification in the various age and sex groups. The value of the survey consists not only in the number of cases found but in the knowledge gained as to the state of infection in almost all children, and in the accumulation of roentgenograms of nearly all the inhabitants over 14 years of age.—*Tuberculosis Case-Finding Survey of the Total Population of Reykjavik, Iceland, 1945*, S. Sigurdson & O. P. Hjaltested, *Publ. Health Rep.*, Nov., 1947, 62: 1593.—(O. Pinner.)

**Tuberculosis in Denmark.**—The author, Theodore Madsen, delegate from Denmark, presented the report here summarized to the permanent committee of the International Office of Public Hygiene at its session in May and June, 1946. From 1876 to 1945, Denmark had a very high tuberculosis death rate, about 30 per 10,000 population. This has gradually diminished since 1890 except for a temporary increase during the first World War. The gradual decrease over the years he attributes in part to improved hygiene and to laws established in 1905 to combat tuberculosis, including the establishment of sanatoriums (one bed for every 1,000 inhabitants), free treatment, and other measures. Useful as they were, these measures had less effect in the reduction of the tuberculosis death rate



than the improved nutrition and housing of the population. During the last World War the death rate did not go up, probably because there was no especial scarcity of food. It did not however continue to fall, after the war, the author thinks, on account of the arrival in Denmark of infected individuals from Germany. He reviews also a tuberculosis survey made in 1933. Extensive tests were made using the intracutaneous method (Mantoux). Old Tuberculin and PPD were used, 0.01 mg. and 1 mg. of the former and 0.005 mg. and 0.05 mg. of the latter, units adopted in 1938 by the Commission on Biologic Standards (League of Nations). The survey began with the examination of school children. At once marked differences were noted in different regions, and it was soon recognized that they were related to the prevalence of bovine tuberculosis. This was then wide-spread especially in the South Jutland. On the other hand, there were areas where it had practically disappeared due to the method of vaccination promoted by Bernhard Bang. In the island of Bornholm in the Baltic Sea, there has been no bovine tuberculosis for several years. There, only 7 per cent of positive tuberculin reactions were obtained in children seven years of age, and only 15 per cent in children 15 years of age. On the other hand, in the village of Haderslev in South Jutland, 45 per cent of the children reacted at 7 years of age, and 75 per cent at 14 years. The mortality, and new clinical cases, surprisingly enough, were almost the same in the two places. The author believes that in Jutland the children received protective vaccination by drinking milk from tuberculous cows, providing the cows did not have mammary or other type of advanced tuberculosis. Continued efforts are being made, however, to eliminate bovine disease. In the course of the examination of different population groups, it was found that new cases of progressive tuberculosis were rarely found in persons who had had positive tuberculin reactions, but that those with negative reactions were more likely to develop clinical disease when exposed to infection. The author

BCG. The fight against tuberculosis prosecuted vigorously in Denmark. The armament consists of a network of dispensaries, dispensaries and mobile X-ray units. Gradually the entire population has been reached. Sources of infection are being isolated. Individuals with negative reactions to tuberculin are being vaccinated with BCG. The number of children in Copenhagen who have positive reactions has decreased from 12 per cent in 1940 to 6 per cent in 1947. In conclusion, the author says the best way to concentrate attention on that part of the population which presents negative reactions to tuberculin and to consider the remaining individuals as ready immunized. There may be some question whether such a plan would be justified in the case of resistance of Danes, who have already been infected, should in the future be diminished by undernutrition or overcrowding.—*Tuberculose au Danemark, T. Madsen, Brit. J. Tuberc., April, 1947, 1: 201.*—(A. T. Laird)

**Tuberculin Test Methods.**—The results of tuberculin tests were 706 West African native school children and 69 tuberculosis contacts. The results were given both Patch and Mantoux tests. The results of 0.1 mg. of Old Tuberculin). Positive reactions were obtained by Patch in 59.9 per cent and by Mantoux in 65.2 per cent. Control reactions were found in 79 cases (100 per cent); this includes 19 cases in which the patch test gave a plaster reaction. The author concludes that the patch test is good for screening provided that Mantoux tests are used for the cases showing negative results.—*Tuberculin Test: A Comparison of the Patch Test and the Mantoux Test in West African Natives, R. B. T. Baldwin, Brit. J. Tuberc., July, 1947, 41: 59.*—(A. G. Cohen)

**BCG Vaccination.**—A ten-year study of the result of BCG vaccination in human beings was carried out by the Tice Laboratory, the Clinic of the Chicago Municipal Sanitary Department and the University of Illinois College of Medicine. Controls were represented by individuals similar to the vaccinated one. The results of isolating the vaccinated and

the tuberculin test became positive was practiced when tuberculosis was present in the household. The following groups were studied: *Group I*—2,831 newborn infants living in the poorest districts of Chicago but not in household contact with tuberculosis. The rate of tuberculosis per thousand person-years was 3.31 times as great in the controls as in the vaccinated. There was one death in the vaccinated group against 7 in the controls. In 1,159 siblings the tuberculosis rate per thousand person-years was 5.29 times as great in the controls as in the vaccinated. There was a suppression of virulent infection in the vaccinated group, but when infection with virulent organisms did occur, the lesions were less extensive, of shorter duration and calcified earlier than the lesions in the nonvaccinated group. *Group II*—256 newborn infants of tuberculous parents. Isolation was practiced for the controls and vaccinated alike. This group was followed for six years. There were two cases of tuberculosis in the vaccinated as compared to 5 in the controls. There were 4 deaths in the controls and none in the vaccinated. *Group III*—student nurses. In 142 vaccinated nurses no case of pulmonary tuberculosis developed over a period of seven years. In 199 controls 3 cases developed. There were 3 additional cases in tuberculin-positive reactors. *Group IV*—medical students. In 109 vaccinated students no case of pulmonary tuberculosis developed. Four cases were reported in the controls. *Group V*—children in a housing project. In 699 vaccinated children there was no case of tuberculosis while in 625 controls there were 4 cases. In 275 tuberculin positive reactors there were 2 cases. *Group VI*—35 tuberculin-negative inmates at a mental institution. In 20 vaccinated inmates no case of tuberculosis developed over a period of four years. In 15 controls one case of bilateral minimal arrested pulmonary tuberculosis was found. The multiple puncture method of vaccination was used. Practically no complications were seen. Following vaccination at birth the tuberculin reaction became 96.6 per cent at the end of one month. In young adults 90 per cent reacted to 1.0 mg.

in two weeks. A positive tuberculin reaction following a single vaccination was present in 92.6 per cent after three and one-half to four years in children vaccinated at birth and 88.6 per cent in student nurses at the end of their training, three years after vaccination.—*BCG Vaccination in All Age Groups: Methods and Results of a Strictly Controlled Study*, S. R. Rosenthal, Eleanor I. Leslie & E. Loewensohn J. A. M. A., January 10, 1948, 136: 73.—(H. Abeles)

**BCG Dry Glucose Vaccine.**—This is a review of a report by E. N. Leschinskaja in the American Review of Soviet Medicine, February 1946, on experiments by Leschinskaja and Vakengut of the BCG Laboratory, Central Institute of Experimental Medicine, Union of Soviet Socialist Republics. The purpose was to overcome the perishability of the BCG vaccine. It was found that BCG retains its viability better in a 50 per cent glucose solution than in any other medium. After a month of drying, the number of colonies obtained upon inoculation remains constant for several months. The dried vaccines may be stored at room temperature, but the best method for storing is refrigeration. The glucose vaccine emulsifies readily. A standard sterile preparation was obtained; the growth of bacilli from this dry BCG after 16 months of storage is approximately equal to that from a liquid vaccine preserved for 2 months. The dry glucose vaccine, as tested by animal vaccination after preservation for one and one half years, differs very little from fresh liquid vaccine.—*Review of the Immunization Value of the BCG Dry Glucose Vaccine*, (Not signed), Public Health Reports, February 1947, 62: 211.—(O. Pinner)

**BCG Vaccination.**—The adequate employment of BCG for immunization should not consist solely of vaccination. Vaccinated persons must be tuberculin tested repeatedly and protected from infection by tubercle bacilli until they become tuberculin-positive. Nothing is gained by vaccinating tuberculin-positive persons. Even if the test is negative, the

person may be in the incubation stage. If there is a known recent exposure to tuberculosis, it is best to defer vaccination for six weeks, at the end of which time the tuberculin test should be checked. There is no harm in vaccinating tuberculin-positive persons, but this confuses interpretation of the result. The sensitivity thus produced lasts from two to ten years. BCG vaccination provides only relative and not absolute immunity. There is no way to distinguish tuberculin sensitivity produced by BCG from that caused by tuberculous infection. In practice, immunity is considered to last as long as the tuberculin test remains positive.—*The Principles of B. C. G. Vaccination*, A. J. Wallgren, *Lancet*, February 14, 1948, 1 237.—(A. G. Cohen)

**Adenopathy after BCG.**—Four cases are reported in which pulmonary tuberculosis with cavitation was treated with BCG or dead tubercle bacilli administered by intracutaneous scarification on the thigh. These cases showed abscess formation and fistulization of an inguinal lymph node two and one-half months after scarification. Spontaneous regression and closure of the fistula occurred within a few weeks. There was no bacteriological evidence of secondary infection. The development of a caseous abscess after intracutaneous administration of BCG or dead tubercle bacilli is considered an exceptional occurrence since it was found only in these 4 cases among about 1,000 scarifications.—*Adenopathies suppurées produites par applications de B.K. morts ou de BCG sur scarifications cutanées*, E. Coulaud, *Rev. de la tuberc.*, 1947, 11 341.—(V. Leites)

**Multiple Puncture BCG Vaccinating Lancet.**—This apparatus contains 40 phonograph needles soldered into a circular brass disc. By release of a spring the needles are shot through a head plate the necessary distance (adjustable) for adequate penetration of the epidermis. The instrument is 4.3 cm. wide at the plate and the overall length is 12.5 cm. To vaccinate, the needles are shot through a small piece of filter paper or cellophane, wet with the BCG vaccine, into the skin. A successful

"take" would thus consist of 40 tiny papules if read approximately three weeks after vaccination. A serious handicap in mass vaccination with the automatic apparatus is the loss of time in sterilizing between each vaccination. Rapid methods for sterilizing are described. The article includes photo-reproductions of the instrument and the appearance of the "take."—*A Spring-actuated Multiple Puncture Apparatus for BCG Vaccination*, K. Birkhaug, *Am. J. Clin. Path.*, September, 1947, 17 751.—(J. S. Woolley)

**Psychiatry in Tuberculosis.**—One function of a tuberculosis sanatorium is to teach patients a new mode of life. To achieve this effectively requires an understanding of the state of mind of the persons involved. Few patients accept the disease with equanimity. Most are in a mood of mild overt or concealed depression or anxiety. Some put on an attitude of defiance and ultra-cheerfulness. This is only a false front against the same anxiety. The patients may have resentment against physicians, nurses, food, etc. The appearance of these moods depends upon many factors including severity of disease, duration of illness etc. Upon admission to the sanatorium, the patients enter a new world. Their mood is affected by other patients; some frighten, others cheer them. They develop a feeling of dependence upon physicians and nurses which is often hard to shake. Some use the time to broaden their interests; most develop very narrow interests of a strictly local character. They often become childish as a result of the regimentation. In places where mingling of sexes is prohibited, undue interest in the opposite sex is often aroused. In time, they sever themselves from outside interests, at the same time developing stronger ties to the sanatorium and its population. Sanatorium management can be democratic or autocratic. Certain procedures are suggested. Upon admission, the patient should be interviewed by a senior staff physician and given some idea about the nature of the disease, length of treatment, etc. A closer rapport between physician and patient is advised. The overenthusiasm of the altruistic type of pa-

tient should be curbed while the selfish type should be encouraged to do more for others. Initial mild depressions should not be discouraged. Those who conceal their anxiety should be encouraged to voice their fears. The nurses should be trained to understand tuberculous patients. Changes of nurses' assignments should be reduced to a minimum. Absolute bed-rest should never last more than a month. Bedroom amenities such as radio and decorations should be permitted. Compatibility of room-mates is important. Food variety is necessary. Smoking in moderation is permissible unless there is laryngeal involvement. The use of alcoholic beverages is not desirable. Visiting hours two to three times a week are in order, but children should not be allowed to visit. No leave should be allowed for the first four months. For the next two months, leave to destinations within a limited distance is permissible. After six months, leave not exceeding forty-eight hours should be granted to selected good cases. A fair hearing should be granted to all complaints. Stimulating occupational therapy is essential. Upon discharge, a personal interview with a senior physician is called for. Female patients should be cautioned against becoming pregnant within two years and should be given directions as to where suitable contraceptive advice can be obtained.—*The Psychological Aspects of Sanatorium Management*, G. S. Todd & E. Wittkower, *Lancet*, January 10, 1948, 1: 49.—(A. G. Cohen)

**Histoplasmin Sensitivity.**—Intracutaneous tests with PPD tuberculin, coccidioidin and histoplasmin were carried out in 1,220 patients. Ninety-six and six-tenths per cent were sensitive to tuberculin, 58.6 per cent to histoplasmin and 31.1 per cent to coccidioidin. Of the entire group, 528 were followed long enough for complete observation. Of these, 117 had acid-fast bacilli in their sputa or gastric washings and 167 had pulmonary calcifications. The patients who were sensitive to histoplasmin showed a higher percentage of hilar and parenchymal calcifications than a similar group of patients who were sensitive to tuberculin or coccidioidin. Bone marrow

studies in 81 patients who were sensitive to tuberculin did not reveal the presence of *Histoplasma capsulatum*. Cultures of material from lymph nodes of 11 patients with progressive exudative pulmonary lesions, positive histoplasmin and negative tuberculin reaction were negative. One and seven-tenths per cent of the patients were sensitive to histoplasmin only, 0.6 per cent to coccidioidin only, and 33.9 per cent to tuberculin only. The use of the histoplasmin sensitivity test is of little value in the differential diagnosis of pulmonary diseases. There is a possibility of a benign self-limiting infection with *Histoplasma capsulatum* with complete recovery, pulmonary calcifications and sensitivity of the skin to histoplasmin.—*Sensitivity of Skin to Histoplasmin in Differential Diagnosis of Pulmonary Disease*, M. E. Groover, Jr., E. A. Cleve, S. Bornstein, A. G. Rice, A. F. Galloway & C. P. Macaluso, *Arch. Int. Med.*, October, 1947, 80: 496.—(G. C. Leiner)

**Histoplasmin Sensitivity.**—A total of 1,188 students at a college in South Wales were X-rayed. Those with calcification were recalled for skin tests. The allergens used were Old Tuberculin, histoplasmin, oidiomycin and a mixed solution of several other fungus extracts. There were 87 cases which showed calcification, of whom 82 were tested. Of these, 67 were tuberculin positive, 15 were negative, all of these being cases with calcification only at the hilus. All tests with histoplasmin and other fungal allergens were negative. The fact that the negative tuberculin tests were found in patients with hilar calcification suggests possible error in interpreting the films. It is concluded that pulmonary calcification in South Wales is not related to sensitivity to histoplasmin or extracts from certain other fungi.—*Intra-Pulmonary Calcification and Histoplasmin*, B. H. McCracken, *Thorax*, March, 1948, 3: 45.—(A. G. Cohen)

**Phthisiogenesis.**—Three basic questions of phthisiogenesis are submitted to a re-evaluation: (1) Is phthisis determined by the age at which primary infection occurs? (2) Does phthisis occur at a definite stage of tuberculous

infection? (5) Is phthisis of exogenous or endogenous origin? Judging from Paris statistics the authors were unable to confirm the modern theory according to which phthisis is mostly due to a late primary infection. Among 301 autopsies of patients who had died of progressive pulmonary tuberculosis 84 per cent showed the presence of old calcified foci. Only 15.5 per cent had recent, incompletely healed or exacerbated primary lesions. Even in persons between the ages of 20 and 30, 76.7 per cent showed old healed primary foci. In the paragraph dealing with question no. 2 the theory of Ranke is criticized in many of its aspects. The phthisiogenetic rôle of Simon foci is denied. The frequency of an apical onset of progressive tuberculosis ("apex" being defined in a large sense as the upper third of the upper lobe) is not attributed to haematogenous seeding but to a physiological predisposition of the apex in adults to implantation of exogenous tubercle bacilli. This predisposition is partly explained by the anatomical structure of the thoracic cage of the adult in contrast to that of the child. The fact that frequently there is an interval between primary infection and the development of phthisis would seem to indicate the existence of distinct stages of tuberculosis. However, in countries with late primary infection this interval is often entirely absent—a proof that no definite stage has to be reached in order to permit phthisis to develop. Phthisis (defined as progressive pulmonary tuberculosis) develops only in a state of diminished resistance of the host (the essence of which is as yet unknown). This state is not necessarily present at the moment of primary infection. The occurrence of a primary infection and the development of conditions which would permit it to become progressive have no causal connection. (1) They may occur at such distant moments that the primary lesions are already healed. (2) If they coincide primary infection appears from the onset as progressive tuberculosis. (3) They may occur after a certain time-interval when the primary lesions have not yet become healed. It is believed that the controversy regarding the exogenous and en-

dogenous origin of phthisis can be solved by approaching the problem as follows: Progressive tuberculosis can develop in one of three ways: (1) through bacilli acquired very long ago and now originating from healed foci; (2) through bacilli acquired very recently; (3) through bacilli acquired in the past which had produced latent but unhealed lesions capable of giving rise at a given moment to progressive tuberculosis. The authors consider the first variety (development of phthisis from old healed primary foci) as almost nonexistent. Among 251 autopsies of tuberculous patients they found possible exacerbation of the primary complex in only 4.8 per cent of cases. Simon foci were also mostly found sterile in the rare instances when they were present. The existence of the second variety (phthisis from recently inhaled bacilli) is considered beyond doubt. In this group belongs progressive primary tuberculosis or cases in which reinfection leads immediately to phthisis. Autopsy findings in the latter cases show the coexistence of completely healed primary foci with extensive lesions. The greatest emphasis is laid on the third variety—cases in which the penetration of bacilli was not necessarily of recent date but where the latent lesions were not healed at the moment of development of phthisis. It is considered immaterial whether the latent lesions are of the primary type (as in countries with late primary infection) or latent reinfection lesions, which is more frequent in Paris. It is the incomplete healing of these lesions and not their chronological phase which is the determining factor. The incidence of such silent lesions and the possibility of progression into phthisis after a variable time interval has become more widely known with the increasing use of mass X-ray surveys. But the general and local factors determining progression and regression of lesions have so far no scientific explanation. This last variety of progressive tuberculosis would thus be both exogenous and endogenous. Its incidence will be determined only after greater numbers of individuals with latent lesions have been followed for long periods of time. The main conclusion drawn from the

foregoing reflections is the evident great danger that exposure to tuberculous infection represents during the whole life span, and not only in childhood. The great majority of latent foci originate after childhood, their course being most frequently abortive. However, it is those lesions that do not regress and heal which are considered as the main origin of phthisis. The fight against tuberculosis is thus the prevention of infection at no matter what age, a fact not enough emphasized by the endogenists.—*Réalités et incertitudes de la phthisiogenèse*, P. Ameuille & G. Canetti, *Rev. de la Tuberc.*, 1947, 11: 507.—(V. Leites)

**Primary Infection in the Adult.**—Among 330 student nurses between the ages of 19 and 25 who entered the Lyon nursing school from 1936 to 1943, 116 were found to have a negative tuberculin reaction on initial examination. This group of nonreactors was followed throughout the training period and as late as 1947. There was a definite increase in the incidence of negative reactions on entry since 1936: 33 per cent in 1937, 44 per cent in 1943, 55 per cent in 1946. The follow-up consisted of X-rays and tuberculin tests (Pirquet method) at four-month intervals. Ninety-two (80 per cent) of the initially negative reactors left school with a positive tuberculin test. Among these 92 cases, 60 per cent had acquired their primary infection within the first eight months, 80 per cent after one year, 90 per cent after eighteen months and 100 per cent after thirty months. The subsequent fates of these student nurses who had converted their tuberculin reactions in hospital surroundings (except on tuberculosis services) were studied. (1) In 71 cases (75.5 per cent) the primary infection appeared at the onset very benign, either completely silent or with very slight symptoms such as transient asthenia or weight loss. In this group there was one postprimary accident, a miliary tuberculosis developing four months after conversion. Further follow-up revealed 4 cases of late "tertiary" tuberculosis of the infiltrative or cavernous type appearing three to five years after conversion. (2) Eight cases (7.5 per

cent) developed manifest primary tuberculosis in an acute form with fever of ten to fifteen days' duration. Among these 8 cases there were 2 deaths due to post-primary progression of disease (one case of miliary tuberculosis and one case of tuberculous meningitis). This group showed no late pulmonary involvement. (3) Fourteen cases (15 per cent) developed primary tuberculosis with severe symptoms and high fever, with or without erythema nodosum. Subsequently 4 cases developed post-primary manifestations such as pleurisy and pulmonary infiltrations of the type of epithelioid tuberculosis. Only one case of tertiary phthisis developed three years after tuberculin conversion. These statistical data seem to indicate that there is a correlation between clinical severity of the primary infection and the incidence of postprimary manifestations in the immediate future. In the group of primary infections with moderate and severe symptoms the incidence of postprimary manifestations was 27 per cent with 2 deaths. In the latent or clinically benign forms of primary infection there was only one case of postprimary involvement (1.4 per cent). The above statistics do not show any correlation between clinical severity of primary infection and the subsequent occurrence of "tertiary" tuberculosis. The group of 214 student nurses with positive tuberculin tests on entrance into training showed not a single pathological incident related to tuberculosis during a follow-up period of seven years.—*La primo-infection tuberculeuse de l'adulte en milieu hospitalier et ses suites tardives*, J. Brun & M. Planchu, *Rev. de la tuberc.*, 1947, 11: 356.—(V. Leites)

**Healing of Tuberculous Foci.**—When tuberculous infection of lung tissue occurs, the reaction will be either exudative, exudative-productive, or purely productive. This depends predominantly on the immunological balance of the individual and is not the subject of the present study. The author attempts to analyze the physico-chemical and physical forces which play a rôle in healing of predominantly exudative foci. He chooses the example of a 2

mm. focus with a caseous center in which there are dead cells, fibrin, and dead and/or living tubercle bacilli. This focus is surrounded by a coat of specific granulation tissue containing epithelioid cells and sometimes giant cells, and around this a nonspecific zone of apposition is formed, as if it were around a foreign body. After central necrosis has occurred, hetero- and autolysis split the protein molecules until the colloids reach the size of electrolytes. When this has occurred, the products can be disposed of according to the normal processes of diffusion into the blood and lymph channels. The connective tissue capsule surrounding the caseous center can be thought of as a semipermeable membrane to which the Donnan equilibrium may be applied. The electrolytes and diffusible colloid substances will be transported to one side of the membrane in an effort to maintain neutrality against the nondiffusible substances remaining in the center. An enzymatic cleavage progresses in the center, more and more cleavage products are transported to the periphery and disposed of in the environment on the other side of the membrane. Clearly then, the whole process is dependent on the speed of the enzymatic break-down. Although ordinarily native body proteins prevent the deposition of insoluble calcium salts, this does not obtain in the center of the necrotic mass where no living proteins are found. Also, no carbon dioxide is produced there as it is in living tissue, and the result is precipitation of insoluble calcium carbonate, sulfate, and phosphate. Calcification thus takes place. Obviously, then, calcification is a process which is in no way specific for tuberculosis, but it obtains wherever a necrotic center is surrounded by a connective tissue capsule so that a basis for Donnan's equilibrium is established. Calcification can be thought of as a fortunate chemical accident. Only when the formerly necrotic center has been inactivated from a toxic-chemical and bacterial point of view does organization by fibroblastic and connective tissue activity take

place. There is ample evidence to indicate that caseous tissue itself contains no capillaries, and the palisade arrangement of fibroblasts around an active tuberculous focus cannot be interpreted as evidence of "invasion" by granulation tissue. It is only evidence that the dead and dying fibroblasts are passively arranged in the line of least resistance, as if sucked in by a funnel. As to the purely physical factors concerned in the healing process, it can readily be seen that the surface of a tuberculous focus does not increase in size nearly as rapidly as its volume with increasing diameter (if the focus be thought of as a ball). Healing is therefore not only absolutely but also relatively faster in small foci.—*Physische und physiko-chemische Faktoren bei der Ausheilung tuberkulöser Herde in den Lungen*, A. J. M. Lohman, *Schweiz. med. Wchnschr.*, July 26, 1947, 77: 802.—(H. Marcus)

**Gas Embolism in Brain.**—Three cases of cerebral gas embolism developed among about 8,000 pneumothorax fillings (0.025 per cent) performed in a Rio de Janeiro tuberculosis hospital. The 3 patients recovered in a period varying from two to eighteen days. Treatment was, according to Amorim-Castel Branco's method, with ergotamine tartrate intramuscularly immediately after symptoms became apparent, one single dose of 0.25 to 0.5 mg. being given. Acetylcholine was also used in the most serious case until all signs of the embolic process subsided. This case also demonstrated that a gas embolus may remain unabsorbed over twenty-four hours in the lumen of the vessel. In such cases absolute bed-rest, preferably in the Trendelenburg position, should be enforced. In opposition to the outcome in this series, the fatality rate in the literature is placed at 10 per cent.—*Conduta terapêutica nas embolias gasosas cerebrais*, S. Rubens Barbosa, *Clin. fisiol.* (Rio de Janeiro), January-March, 1947, 2: 88.—(A. A. Moll)

# PROTECTIVE VACCINATION AGAINST TUBERCULOSIS WITH SPECIAL REFERENCE TO BCG VACCINATION<sup>1</sup>

JOSEPH D. ARONSON<sup>2</sup>

## INTRODUCTION

Much of the modern conception of active immunization against tuberculosis stems from the original, and now historical, observations of Jenner (1), who in 1796 proved the protective value of cowpox against smallpox. The subsequent classical studies of Pasteur firmly established and extended the knowledge regarding the effectiveness of modified or attenuated bacteria and viruses as immunizing agents.

When Koch (2), in 1882, discovered the specific organism of tuberculosis, the way was opened for basic investigations dealing with the prevention and treatment of this disease.

That the body once infected with the tubercle bacillus resists reinfection was suggested by the observations of Marfan (3). He noted that pulmonary tuberculosis was rare among those who presented evidence of healed lupus or healed tuberculous cervical adenitis. Further evidence that the body of a previously infected animal resists reinfection was indicated by the observations of Koch (4). He noted that the introduction of tubercle bacilli into the tissues of a tuberculous guinea pig elicited an acute, intense, local inflammatory reaction with sloughing and no significant enlargement of the regional lymph nodes. Conversely, in normal guinea pigs the introduction of the same number of tubercle bacilli caused only a slight immediate reaction, but was followed in approximately two weeks by the development of a nodule which ulcerated. The regional lymph nodes enlarged and caseated and the tuberculous process progressed until death occurred. The failure of some investigators to confirm these observations of Koch was probably due to a low degree of sensitivity in their infected animals.

## *Review of Literature*

The hope that tuberculin discovered by Koch (5) might have some protective value was never realized. Similarly other extracts of the tubercle bacillus and metabolic products of the organism have failed as immunizing agents.

Repeated attempts have been made by different investigators to immunize against tuberculosis by means of tubercle bacilli modified or killed by different chemicals. Among some of the chemicals employed for this purpose have been

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<sup>2</sup> From the Health Division, Office of Indian Affairs, Department of the Interior, Washington, D. C.; the Henry Phipps Institute, University of Pennsylvania, Philadelphia; and the Tuberculosis Control Division, U. S. Public Health Service.



formalin, sodium hypochlorite, glycerine, urea, galactose, neurine, choline, sodium oleate, lactic acid, saponin, and trichlorethylene. In most instances such modified tubercle bacilli have given slight, if any, immunity.

Tubercle bacilli, modified by the action of radium emanations or by ultraviolet light, have been used experimentally to protect against reinfection. Bisceglie (6) found that the human type tubercle bacillus which had been exposed for one to forty-eight hours to 5 mg. of radium bromide became granular, lost its acid-fast property and became attenuated. Guinea pigs treated with such modified tubercle bacilli reacted to tuberculin eighteen days after injection and showed definite resistance to reinfection with virulent bacteria. Smithburn and Lavin (7) found that tubercle bacilli in a concentration of 1.0 mg. per cc. exposed to ultraviolet light in the range of 2,537 Å for nine minutes remained viable, became attenuated, and induced resistance to reinfection in guinea pigs. In contrast, cultures exposed for ten minutes to ultraviolet light were killed and lost their immunizing properties. Olson, Habel and Piggott (8) claim that 3 doses of human tubercle bacilli, killed by ultraviolet light, protected guinea pigs against reinfection to the same degree as did a single dose of viable BCG vaccine.

The effectiveness of heat-killed cultures in increasing resistance to tuberculosis is indecisive. The experimental studies of Langer (9, 10), Petroff and Stewart (11), Petroff, Branch and Jennings (12), Lange, Jochimsen and Magat (13), Opie and Freund (14), and others indicate that animals treated with heat-killed tubercle bacilli develop increased resistance to reinfection with virulent tubercle bacilli. On the basis of the results obtained in experimental animals, Langer (9), Zadek and Meyer (15), and Goodwin and Schwentker (16), have employed heat-killed tubercle bacilli to immunize children against reinfection. A study of the effectiveness of heat-killed tubercle bacilli in the control of tuberculosis was conducted by Opie, Flahiff and Smith (17) in an institution having a high morbidity and mortality from tuberculosis. Heat-killed tubercle bacilli were injected into 210 tuberculin-negative persons while 206 tuberculin-negative persons served as controls. During the first three years of observation, 23 cases of tuberculosis developed among the vaccinated, 15 of whom died from this disease, while 39 cases of tuberculosis, including 23 deaths, occurred among the controls.

Attempts to increase resistance by the use of cultures of tubercle bacilli attenuated by aging were first made by Dixon (18) in 1889. He employed old cultures which contained numerous pleomorphic acid-fast bacilli to immunize guinea pigs, rabbits and opossums. Details of these experiments are lacking.

The immunizing property of various heterologous strains of tubercle bacilli has been studied. MacFadyean, Sheather, Edwards and Minett (19) found that resistance to tuberculous infection was less marked in cattle injected with the avian type of tubercle bacilli than in those treated with viable human type bacilli. The use of the avian type for the vaccination of cattle is dangerous for the organism can be eliminated in the dejecta and carried by birds over widespread areas. Römer (20) failed to demonstrate any increase in resistance in

guinea pigs treated with viable avian type bacilli. In 1937, Wells (21) isolated an acid-fast pleomorphic bacillus from lesions of spontaneous tuberculosis from the wild vole (*Microtus agrestis*). This murine type tubercle bacillus, while highly pathogenic for the vole, produces progressive tuberculosis in guinea pigs only with large doses. It differs in its morphology, cultural characteristics and pathogenicity from other types of tubercle bacilli. It possesses an antigenic structure indistinguishable, however, from the mammalian types of tubercle bacilli. Guinea pigs and cattle injected with this culture have shown increased resistance to reinfection. The injection into man of a vaccine prepared from the viable vole bacillus produces a local ulcer or abscess with no involvement of the regional lymph nodes. From reports by different investigators it is evident that the vaccine prepared from the vole bacillus is safe and that the local reaction does not differ materially from that induced by BCG vaccine. The tuberculin reaction is positive in a high per cent of persons receiving the vole vaccine. The studies thus far do not permit conclusions as to its value in the control of tuberculosis in man. The murine type of tubercle bacillus isolated from the vole may prove of value as an immunizing agent against tuberculosis.

Tubercle bacilli of the poikilothermic type, isolated from cold-blooded animals, have been tried for preventive purposes. Friedmann (22) claimed curative and protective value for an acid-fast bacillus isolated from the pulmonary lesions of two turtles living in the Berlin aquarium. Saenz (23) found that the cultural characteristics and antigenic structure of this organism (*M. chelonae*) resembled those of the acid-fast saprophytes. It did not produce a Koch phenomenon in tuberculous animals, nor in animals treated with the homologous culture. It did not produce tuberculin. Saenz (23), as well as Libbertz and Ruppel (24) and other investigators, could not demonstrate any significant increase of resistance to tuberculous infection in animals treated with this culture. Weber and Titze (25) found that tubercle bacilli isolated from cold-blooded animals did not appreciably increase resistance of cattle to infection with virulent tubercle bacilli. More recently, Aronson (26, 27) found no increase in resistance to reinfection with the human type tubercle bacillus in guinea pigs treated with recently isolated viable cultures of *M. marinum* or *M. thamnophaeus*. These cultures were isolated from fish and from garter snakes respectively.

Attenuation of mammalian tubercle bacilli by passage through cold-blooded animals was attempted by Klimmer (28). He made repeated passages of both bovine and human types of tubercle bacilli through various cold-blooded animals but especially salamanders. A mixture of such modified organisms and human type of tubercle bacilli, heated to 52-53°C., was designated as "Antiphymatol" and was recommended for vaccination against tuberculosis. Whether the acid-fast bacilli recovered from the cold-blooded animals were the original bovine and human type of tubercle bacilli, or were acid-fast saprophytes commonly found in swamps or in cold-blooded animals, is difficult to determine. According to Eber (29) the vaccine has no immunizing value.

Much of the early work dealing with immunization of animals, and especially of cattle, gave no conclusive results. This was in part due to the failure to

recognize at that time that the human and bovine types of tubercle bacilli were distinct types. When Theobald Smith (30) demonstrated that mammalian tubercle bacilli differed from each other in their cultural characteristics, biochemical reactions, and virulence for certain animals, especially cattle and rabbits, it became possible to estimate the immunizing value of each type. With the recognition that the human type tubercle bacillus tends to localize in cattle and other animals and does not produce generalized tuberculosis, attempts were made to immunize cattle by the administration of this type of tubercle bacilli.

Among the first to use the human type were Pearson and Gilliland (31). In 1902 they injected cattle intravenously with viable human tubercle bacilli and found that these animals developed increased resistance to a challenge dose of virulent bovine bacilli. Neufeld (32) injected animals first with increasing amounts of viable human bacilli and subsequently with viable bovine type tubercle bacilli. He found that such treated animals developed definite resistance to reinfection, while those treated with dead tubercle bacilli showed no increased resistance. Neufeld (32) also observed that some animals, and especially goats, which had survived repeated intravenous injections of tubercle bacilli, frequently died within twenty-four hours with symptoms of shock following such injections.

Von Behring (33) produced a vaccine for immunizing cattle which he termed "Bovovaccine". This vaccine consisted of a viable human type tubercle bacillus attenuated by repeated transplantation on glycerine broth over a period of six years and further attenuated by drying the bacilli in vacuo. The results from its use lacked uniformity because of variations in the virulence of the vaccine. The majority of investigators were agreed that "Bovovaccine" increased the resistance of cattle to reinfection with virulent bovine strains. This resistance, although not absolute, reached its maximum in about three months after vaccination, but decreased after one year. Koch, Schutz, Neufeld and Miessner (34) developed a vaccine consisting of a mixture of viable human and bovine tubercle bacilli which they termed "Tauruman". This vaccine, which was administered intravenously to cattle, contained viable virulent tubercle bacilli which lodged in the lymphatic system of the animals. Weber and Titze (35) concluded that this vaccine gave a more uniform degree of protection than did Von Behring's "Bovovaccine".

The use of viable virulent tubercle bacilli for immunizing cattle was found to be a dangerous procedure and therefore could not be recommended for vaccination. Titze (36) observed that cattle treated with "Tauruman" eliminated in their milk and dejecta viable virulent tubercle bacilli from this vaccine. Similarly, Griffith (37) found that goats and cattle injected with viable virulent human type tubercle bacilli excreted these organisms in their milk over a long period of time.

Webb and Williams (38) showed that resistance to tuberculous reinfection could be induced in animals as sensitive as the guinea pig and monkey by injecting them with increasing numbers of viable virulent tubercle bacilli. On the

basis of their experimental studies, they injected two children with increasing numbers of viable tubercle bacilli beginning with an initial dose of one organism. After twenty years these children were living and well (39). Moeller (40) vaccinated several tuberculin negative children by rubbing viable virulent tubercle bacilli into the scarified skin. Selter (41) injected nine young children with increasing amounts up to 100,000 of viable virulent bacilli. No conclusions can be drawn from these studies because of the small number of subjects and the inadequacy of the reports of the results. The use of viable virulent tubercle bacilli must be considered as a dangerous procedure.

The use of tubercle bacilli attenuated by prolonged cultivation on an artificial medium was first described by DeSchweinitz (42). He observed significant attenuation of a culture of tubercle bacillus which had been grown on glycerine broth for fourteen generations. After the seventeenth generation on this medium, the culture was no longer pathogenic for guinea pigs. Nevertheless, guinea pigs treated with this attenuated strain reacted to tuberculin and showed increased resistance to reinfection. Cultures of tubercle bacilli which have undergone spontaneous attenuation have been used extensively in experimental studies on immunity. One of the best known of such strains is the R 1 human type, originally isolated by Trudeau in 1891. This culture underwent spontaneous attenuation in virulence two years following its isolation (43). The classic studies of Krause and Willis (44, 45, 46) and of Willis (47, 48) on the mechanism of resistance proved that resistance to reinfection with virulent tubercle bacilli followed the use of the attenuated viable R 1 strain.

Calmette and Guérin (49) reported the attenuation of a virulent bovine strain of tubercle bacillus originally isolated by Nocard in 1902 from the udder of a tuberculous cow. This culture was originally designated as "souche lait Nocard." In 1908 this culture produced fatal tuberculosis in guinea pigs inoculated with 0.0001 mg. Beginning that same year, the culture was transplanted to potato medium containing beef bile. After 230 transplantations on this medium extending over a period of thirteen years, this organism no longer produced progressive tuberculosis when injected into animals as susceptible as the guinea pig. Despite the loss of virulence, this strain, designated BCG or the Bacillus of Calmette and Guérin, has retained its original staining characteristics, its original cultural and biochemical properties, and its ability to produce potent tuberculin. Introduced into the usual laboratory animals it produces histological tubercles which remain localized. Injected into these animals, it is innocuous, induces the formation of specific humoral antibodies and gives rise to increased resistance to tuberculous reinfection. It is true that inoculation with BCG does not fully protect guinea pigs against reinfection, but the inoculated animals live much longer and the severity of the lesions is less marked than in the control animals.

*Summary:* The above survey is a brief review of the many diverse preparations which investigators have used for specific immunization against tuberculosis. The conclusions from this review of the literature are that Old Tuberculin or the metabolic products of the tubercle bacillus have no value

in increasing resistance to reinfection and that tubercle bacilli, modified or killed by the action of chemicals, may give slight or transitory immunity in animals. Tubercle bacilli exposed to radium emanations or to ultra violet light gave promising results only if the organisms remained viable after such exposure. Heat-killed bacilli, in more recent experiments in animals and man, have given suggestive, if not entirely convincing, results. The results from the use of heterologous types of mammalian tubercle bacilli to protect cattle from reinfection with bovine bacilli have varied. The immunizing power of strains of acid-fast bacilli isolated from cold-blooded animals has been questionable, and that of the avian strain, slight and transitory. The human type organism, aside from the danger in its utilization, does produce immunity in cattle of about a year's duration. The murine type of organism, isolated from the vole, seems to have definite value in increasing resistance to reinfection. A great mass of investigation in both animals and man indicates that viable tubercle bacilli, either virulent or attenuated, produce the best and most lasting protection. The use of viable virulent organisms in man is an unsafe procedure.

*Mechanism of development of increased resistance:* Many observers have speculated on the mechanism of the development of increased resistance to reinfection in man and animals. Experimental and clinical evidence is in general agreement that increased resistance develops in the course of a primary or initial infection with tubercle bacilli. Römer (20) concluded that increased resistance is associated with the development of an anatomical tubercle. Hamburger (50) concluded that a primary tuberculous infection alters the reactivity of animals so that a subsequent infection with a large dose may kill, a smaller dose may induce a severe local reaction, while minute amounts fail to produce a reaction. His studies indicate that persons reacting to tuberculin possess a certain degree of resistance to reinfection with small doses of virulent tubercle bacilli. Calmette and Guerin (51), in their extensive studies on the immunization of cattle, emphasize that certain factors aside from dose and virulence play an important role in tuberculous infection and resistance. They noted that a single dose of finely divided virulent tubercle bacilli produced a tuberculous process which tended to heal and that the animals thus treated gave a positive reaction to tuberculin and showed increased resistance to reinfection. In contrast, repeated infections at short intervals with viable virulent tubercle bacilli resulted in a process which caseated and progressed.

*Introduction of BCG vaccinations:* The conclusions of Calmette and Guerin that resistance to reinfection was due to the presence of viable tubercle bacilli led them to the use of an attenuated strain of tubercle bacillus which they designated as *Bacillus Calmette-Guerin* (BCG). The results obtained by injecting cattle with BCG vaccine were such as to suggest its use as a protective vaccine in man. In July 1921, Weill-Halle (52) administered this vaccine per os to a newborn infant. No untoward results followed its administration and within a few years the use of BCG vaccine spread rapidly through continental Europe, in the countries of South America, and to Japan. The oral route of administration was recommended as it was believed that the intestinal mucosa

of newborn infants was permeable to the passage of bacteria and that the vaccine would therefore localize and remain in the mesenteric lymph nodes. Calmette's original suggestion was that newborn babies be given 3 doses of 10 mg. each per os, at forty-eight hour intervals.

As the tuberculin reaction continues to remain negative in a high per cent of those vaccinated per os, the vaccine was later administered subcutaneously. This method, however, gave rise to cold abscesses which frequently had to be aspirated or treated surgically. Wallgren (53) advocated the intracutaneous injection of the vaccine. This procedure has been widely used and has been followed by a very high per cent of positive tuberculin reactions. The main objections are that it gives rise to a localized, slowly healing ulcer, and in a small per cent of cases is associated with ulceration of the regional lymph nodes. More recently, Rosenthal (54) has recommended the multiple puncture technique. This consists of making 35 tangential pricks with a sterile needle through a drop of BCG vaccine. He claims that the tuberculin reaction becomes positive in all but a few cases. Birkhaug (55) has devised an apparatus consisting of a metal disk with 40 needles which is actuated by spring pressure. The needles pass through a piece of filter paper saturated with the BCG vaccine and carry the vaccine into the underlying skin.

#### BCG VACCINATION AMONG SOME AMERICAN INDIANS

An opportunity to determine the effectiveness of BCG vaccine in the control of tuberculosis in a population having a high morbidity and mortality from this disease was made possible through the Health Division of the Office of Indian Affairs, Department of the Interior. As this organization was interested in utilizing all available measures to control tuberculosis among the Indians of the United States and Alaska, a cooperative study was undertaken with the Henry Phipps Institute, University of Pennsylvania. Beginning in 1935, certain Indian Agencies were selected on the basis that their populations were accessible, non-migratory, and were cooperative and indigenous to these areas. The study was conducted among the Indians living on the Pima Agency, Arizona; the Wind River Agency, Wyoming; the Turtle Mountain Agency, North Dakota; the Rosebud Agency, South Dakota, and among nonreservation Indians living in twelve towns and villages of southeastern Alaska.

The Indians included in the study differ in their linguistic and racial stocks and in their cultural patterns. They represent the agricultural groups, the Indians of the plains who were historically hunters, the woodland Indian groups, and the Indians of Alaska who lived on and off the sea. Their food habits range from the high carbohydrate diet of the Pima Indians of Arizona, and the high protein diet of the Shoshones and Arapahos of Wyoming and the Rosebud Sioux of South Dakota, to the rich fat diet of the Indians of southeastern Alaska. In their degree of racial purity, they vary from the relatively pure blood Pima tribe of Arizona and the Arapaho of Wyoming, to the Chippewa tribe of the Turtle Mountain Agency, North Dakota, with its marked French-Canadian admixture, and the Shoshone Indians of Wyoming with admixture of French and

other white races. The Indians of southeastern Alaska also are admixed with other races. While these Indians may vary in many particulars, their economic level with few exceptions is uniformly low, housing poor and crowded, and subsistence meager.

### *Morbidity and Mortality from Tuberculosis*

In order to evaluate the role of BCG vaccination in the control of tuberculosis, it was essential to determine the morbidity and mortality from this disease among the general population of each area included in the investigation. These data serve as an index of the intensity of exposure to tuberculosis to which those in this study might be subjected.

The incidence of tuberculous infection was determined during 1935-37 by means of the intracutaneous tuberculin test. An initial dose of 0.00002 mg. of a preparation of Purified Protein Derivative (PPD) tuberculin, prepared by Dr. Florence Seibert of the Henry Phipps Institute, Philadelphia, was used. Those who failed to react to this dose of PPD after forty-eight hours were reinjected with 0.005 mg. of the same PPD. A final reading was made forty-eight hours later. The intensity and character of the tuberculin reactions were recorded. All children attending school were tested with PPD, as were a significant number of unselected preschool children and a small per cent of the older age groups. It was not considered essential to test a larger per cent of the older age group when sampling indicated that practically all those tested reacted to PPD tuberculin. The results of the tuberculin tests among the general population of the different agencies are presented in table 1.

The incidence of tuberculous infection among the Indians in the areas tested rises rapidly with increasing age, exceeding that previously noted among the Negro inhabitants in rural areas of some of the southern states and among white residents in rural areas of Michigan (56). Among Indians, as among Negroes, there is a marked sensitivity to tuberculin, in all probability due to the intensity and frequency of exposure. Of the Indians who were positive to PPD, 91.4 per cent reacted to the first dose of 0.00002 mg. Of these, 55.2 per cent had a local inflammatory reaction exceeding 20 mm. in diameter (3 plus), associated in a small per cent of cases with a systemic reaction.

It will be noted from table 1 that the Rosebud Agency had the highest incidence of tuberculous infection, and that in the 20 to 24 year age group it had reached 100 per cent. The lowest incidence of tuberculous infection occurred among the Shoshone Indians of the Wind River Agency, Wyoming. In this group, 6 per cent of those under 5 years of age reacted to PPD while in the 20 to 24 year group 72 per cent gave a positive reaction.

The incidence of significant pulmonary lesions characteristic of tuberculosis was based on roentgenological examination of the chest of an unselected significant sample of the general population in each area. The per cent of the general population examined roentgenologically during 1936-37 varied for each area but was significant statistically. It will be noted from table 2 that the

highest incidence of pulmonary lesions was found in southeastern Alaska where the morbidity and mortality from tuberculosis has long been known to be high.

*Character of tuberculosis among Indians:* There exists an impression that tuberculosis among Indians runs an acute, progressive course resembling that frequently found among Negroes. Observations during the course of the present study indicate that pulmonary tuberculosis among the Indians resembles that found among the white population. Fibrosis and calcification are common

TABLE 1

*Incidence of tuberculin reaction by Indian agency & age, 1935 to 1937*

| AGENCY               | UNDER 5               |                              | 5 TO 9                |                              | 10 TO 14              |                              | 15 TO 19              |                              | 20 TO 24              |                              |
|----------------------|-----------------------|------------------------------|-----------------------|------------------------------|-----------------------|------------------------------|-----------------------|------------------------------|-----------------------|------------------------------|
|                      | Num-<br>ber<br>tested | Per<br>cent<br>posi-<br>tive | Num-<br>ber<br>Tested | Per<br>cent<br>posi-<br>tive | Num-<br>ber<br>tested | Per<br>cent<br>posi-<br>tive | Num-<br>ber<br>tested | Per<br>cent<br>posi-<br>tive | Num-<br>ber<br>tested | Per<br>cent<br>posi-<br>tive |
| Pima.....            | 410                   | 11.4                         | 628                   | 23.0                         | 478                   | 48.5                         | 259                   | 77.2                         | 136                   | 89.7                         |
| Shoshone.....        | 81                    | 6.2                          | 103                   | 24.2                         | 92                    | 56.5                         | 59                    | 83.1                         | 46                    | 71.7                         |
| Arapaho.....         | 127                   | 7.0                          | 122                   | 42.6                         | 115                   | 70.4                         | 82                    | 85.4                         | 41                    | 97.5                         |
| Rosebud.....         | 100                   | 25.0                         | 582                   | 45.9                         | 721                   | 65.6                         | 409                   | 84.6                         | 14                    | 100.0                        |
| Turtle Mountain..... | 0                     | —                            | 100                   | 38.0                         | 120                   | 71.6                         | 296                   | 91.2                         | 128                   | 90.6                         |
| Alaska.....          | 533                   | 14.2                         | 609                   | 39.5                         | 453                   | 67.1                         | 116                   | 71.5                         | 9                     | 100.0                        |

TABLE 2

*Per cent significant pulmonary tuberculous lesions by agency, 1936 to 1938*

| AGENCY        | TOTAL<br>POPULATION | EXAMINED ROENTGENOLOGICALLY |          | TUBERCULOUS<br>LESIONS |
|---------------|---------------------|-----------------------------|----------|------------------------|
|               |                     | Number                      | Per cent | Per cent               |
| Rosebud.....  | 7,994               | 2,450                       | 30.6     | 3.1                    |
| Wind River:   |                     |                             |          |                        |
| Shoshone..... | 1,026               | 574                         | 55.9     | 5.7                    |
| Arapaho.....  | 1,164               | 740                         | 63.6     | 5.8                    |
| Pima.....     | 4,841               | 2,060                       | 42.5     | 1.1                    |
| Alaska.....   | 5,000               | 3,897                       | 77.6     | 6.9                    |

and the disease in many instances runs a long chronic course, even in cases of moderately or far advanced tuberculosis. That tuberculosis among Indians has undergone a change in character is evident from the early reports of missionaries, explorers and doctors. These reports call attention to the high incidence of extrapulmonary forms of tuberculosis, especially scrofula. The prevalence of tuberculosis among Indians was investigated by the Office of Indian Affairs in 1904. It was found that among an Indian population of 107,000 persons, 2,836 cases were diagnosed as tuberculous. Of this number 1,038 were pulmonary in nature, 208 were cases of tuberculosis of the bones and joints, while 1,590 were cases of tuberculosis of lymph nodes. Several of the medical officers who have long been active in studying and treating tuberculosis among



Indians have kindly given their views to the writer. Doctor A. J. Wheeler (57), after more than thirty-five years of experience, reports that he no longer sees the large masses of cervical nodes common in his early years of service. His impression is that large, thick-walled cavities are less common among the Indian patients of the Phoenix Indian Sanatorium than among the white patients in Arizona. Doctor Ralph M. Alley (58) of the Indian Service also states that he no longer sees many cases of extrapulmonary forms of tuberculosis. Examinations of the chest roentgenograms of the older Indians, who present cervical scars as evidence of extrapulmonary forms of tuberculosis, show that in approximately 25 per cent of the cases there is evidence of previous pulmonary involvement indicated by fibrosis and calcification. Doctor Alley states that he has

TABLE 3

*Death rate per 100,000 from all causes and from tuberculosis by agency and year*

| YEAR | WIND RIVER AGENCY |                        |              | ROSEBUD AGENCY   |                        |              | PIMA AGENCY      |                        |              | TUMBLE MOUNTAIN AGENCY |                        |              |
|------|-------------------|------------------------|--------------|------------------|------------------------|--------------|------------------|------------------------|--------------|------------------------|------------------------|--------------|
|      | Total population  | Death rate per 100,000 |              | Total population | Death rate per 100,000 |              | Total population | Death rate per 100,000 |              | Total population       | Death rate per 100,000 |              |
|      |                   | All causes             | Tuberculosis |                  | All causes             | Tuberculosis |                  | All causes             | Tuberculosis |                        | All causes             | Tuberculosis |
| 1935 | 1,979             | 2,375                  | 657          | —                | —                      | —            | 5,866            | 2,727                  | 442          | —                      | —                      | —            |
| 1936 | 2,033             | 2,607                  | 383          | —                | —                      | —            | 5,908            | 2,353                  | 237          | —                      | —                      | —            |
| 1937 | 2,104             | 3,660                  | 618          | —                | —                      | —            | 5,854            | 2,425                  | 307          | —                      | —                      | —            |
| 1938 | 2,121             | 2,688                  | 377          | 7,921            | 2,171                  | 520          | 5,993            | 1,836                  | 200          | —                      | —                      | —            |
| 1939 | 2,190             | 2,009                  | 365          | 7,994            | 1,801                  | 400          | 6,094            | 1,936                  | 164          | 3,287                  | 2,038                  | 304          |
| 1940 | 2,230             | 2,511                  | 493          | 8,070            | 1,425                  | 259          | 6,093            | 1,428                  | 148          | 3,419                  | 1,180                  | 292          |
| 1941 | 2,289             | 2,780                  | 165          | 8,127            | 1,279                  | 443          | 6,236            | 1,750                  | 229          | 3,483                  | 1,610                  | 373          |
| 1942 | 2,348             | 2,044                  | 426          | 8,203            | 1,413                  | 280          | 6,399            | 1,750                  | 172          | 3,572                  | 672                    | 54           |
| 1943 | 2,262             | 1,680                  | 221          | 8,279            | 1,920                  | 398          | 6,479            | 1,394                  | 108          | —                      | —                      | —            |
| 1944 | 2,334             | 2,785                  | 257          | 8,355            | 1,627                  | 323          | 6,632            | 1,598                  | 286          | 3,738                  | 803                    | 0            |
| 1945 | 2,376             | 1,851                  | 210          | 8,532            | 1,289                  | 363          | 6,745            | 1,823                  | 89           | 3,845                  | 806                    | 78           |
| 1946 | 2,438             | 1,558                  | 246          | —                | —                      | —            | 6,745            | 1,734                  | 133          | —                      | —                      | —            |

not observed any significant difference between the course or character of tuberculosis among Indians and of the disease observed in the white population, and that the Indian responds well to treatment. The late Doctor L. W. White (59), who spent more than thirty years among the Indians, believed that miliary tuberculosis was much less frequent than formerly.

As the mortality rate from tuberculosis reflects the incidence of clinically manifest cases of this disease in the ratio of approximately nine cases for each death, it can be used as an index of the extent and intensity of possible exposure in a community. This information was compiled from the available records of each agency for the different years and is summarized in table 3.

The foregoing data indicate, in as objective a manner as possible, the high incidence of tuberculous infection and the high morbidity and mortality from tuberculosis in the populations studied. It must be realized that frequently Indians with clinically manifest tuberculosis refuse to go to a sanatorium for

treatment, or, if they do go, they remain on the average about six months and then return to the Agency, attend public meetings and athletic events and visit promiscuously other homes in the Agency.

#### PLAN OF INVESTIGATION

*Method for selection of cases:* It is generally agreed that a positive reaction to tuberculin results from a tuberculous infection and is generally interpreted as an indication of increased resistance to reinfection. Therefore, the use of BCG or other immunizing agents is not indicated in those who react to tuberculin. Conversely, specific immunization with BCG vaccine is indicated in those who have escaped natural infection and who therefore fail to react to tuberculin. The parenteral administration of BCG vaccine results in the production of a self-limited primary local lesion which may involve the regional lymph nodes and is followed by specific allergy, as measured by the tuberculin test.

To eliminate or minimize any bias in the selection of cases for this study, all children attending the Indian Service schools and the denominational boarding schools, and as many children of preschool age as possible, were tested with tuberculin PPD. Of those tested, a total of 3,008 persons, ranging in age from less than one year to 20 years, living on the different Agencies and in southeastern Alaska, failed to react to the intracutaneous injection of 0.00002 and 0.005 mg. of PPD, or gave a doubtful reaction with 0.005 mg. of PPD. These 3,008 persons were selected for the study.

The significance of any controlled study depends to a great degree upon the equality of the samples. The groups studied must be comparable and the selection of members of the groups made without any bias. To meet these requirements a record was prepared for each person who failed to react to tuberculin PPD. All of these records for each school and adjacent area were then sorted by sex and year of birth. An alternate division of the records was then made within each sex and age group. Approximately one-half received the BCG vaccine while the remaining number served as controls. In a small number of instances, the person selected was absent from school and one of those listed for the control group was substituted and the absentee then served as a control. The comparability of the two groups by 5-year age periods and by sex is shown in table 4.

The study was initiated at the Pima Agency, Arizona, in December 1935, and was extended in 1936 to include the Shoshone and Arapaho Indians living on the Wind River Agency, Wyoming, and the Chippewa Indians of the Turtle Mountain Agency, North Dakota. In 1937 and 1938 the Sioux Indians of the Rosebud Agency, South Dakota, and the Indians of southeastern Alaska were added to the study, as well as a second group at the Pima Agency, Arizona.

*Technique of vaccination:* Fifteen hundred and fifty-one persons were injected with one of 13 different lots of vaccine prepared in a portable laboratory at each agency. The BCG culture was maintained on potato medium and was transplanted to bile potato at regular intervals. No other culture was kept in the

laboratory and, to minimize the danger of contamination with tuberculous material, the laboratory was set up in a vacant schoolroom at a distance from the hospital. The vaccine was prepared from cultures of the organism grown on Sauton's synthetic medium for periods varying from seven to thirty days. The bacillary mass was collected from the surface of the medium, the excess fluid removed and the moist bacillary mass weighed and suspended in sterile physiological saline. Those selected for vaccination received an intracutaneous injection of 0.1 cc. of the vaccine containing either 0.1 or 0.15 mg. of the moist bacillary mass. The injections were made as superficially as possible in the skin over the region of the deltoid muscle. The vaccine was used within the first three days of its preparation and in most instances within one day after preparation. At the same time that the vaccine was given, the control group received an intracutaneous injection of 0.1 cc. of physiological saline. Neither vaccinated

TABLE 4  
*Distribution by sex and age of BCG vaccinated and controls*

| AGE IN 5-YEAR PERIODS* | NUMBER      |          |             |          |             |          | PER CENT    |          |             |          |             |          |
|------------------------|-------------|----------|-------------|----------|-------------|----------|-------------|----------|-------------|----------|-------------|----------|
|                        | Male        |          | Female      |          | Total       |          | Male        |          | Female      |          | Total       |          |
|                        | Vacci-nated | Con-trol | Vacci-nated | Con-trol | Vacci-nated | Con-trol | Vacci-nated | Con-trol | Vacci-nated | Con-trol | Vacci-nated | Con-trol |
| Under 5 . . . . .      | 204         | 213      | 229         | 200      | 433         | 413      | 6.8         | 7.1      | 7.6         | 6.7      | 14.4        | 13.7     |
| 5 to 9 . . . . .       | 306         | 322      | 353         | 302      | 659         | 624      | 10.2        | 10.7     | 11.7        | 10.0     | 21.9        | 20.7     |
| 10 to 14 . . . . .     | 191         | 170      | 196         | 181      | 387         | 351      | 6.3         | 5.6      | 6.5         | 6.0      | 12.8        | 11.7     |
| 15 to 19 . . . . .     | 36          | 33       | 36          | 36       | 72          | 69       | 1.2         | 1.1      | 1.2         | 1.2      | 2.4         | 2.3      |
| Total . . . . .        | 737         | 738      | 814         | 719      | 1,551       | 1,457    | 24.5        | 24.5     | 27.0        | 23.9     | 51.5        | 48.4     |

\* Attained age at beginning of study.

nor controls were isolated before or after vaccination, nor was their mode of living modified.

*Reaction at vaccination site:* The character and intensity of the local inflammatory reaction following the intracutaneous injection of BCG vaccine were not affected by sex, degree of Indian blood, or constitutional type. In general the local reaction was less marked among the children of preschool age. The intensity and character of the local reaction vary in man and in guinea pigs with different preparations of the vaccine.

The intracutaneous injection of either 0.1 or 0.15 mg. BCG vaccine was followed forty-eight hours later by the appearance of a sharply defined reddened nodule measuring approximately 4 mm. in diameter and about 1 mm. in height. During the first two weeks following vaccination the local inflammation subsided. Three to four weeks after vaccination the nodule rapidly increased in size and in many instances a definite central area of softening was noted. Ulceration occurred by the fourth week in approximately 75 per cent of cases and persisted for from four to eight weeks. The ulcers healed, leaving small scars averaging 5 to 10 mm. in diameter, which have persisted during the eleven

years of the study. In a high per cent of cases there was noted a sense of fullness in the axilla of the vaccinated side following the injection. In about 5 per cent of the cases the regional lymph nodes along the anterior axillary fold were palpable. In no instance did the lymph nodes ulcerate. Healing of the local ulcer was completed in approximately twelve weeks after vaccination. It was noted that healing of the ulcers was more prompt among the Pima Indians of Arizona and that healing was significantly slower and the ulcers more chronic in nature among the Indians of southeastern Alaska.

Smears prepared from the ulcers at various times showed at first numerous polymorphonuclear cells, occasional large mononuclear cells and numerous clumps of well staining extracellular and intracellular acid-fast bacilli. Later there was noted a significant decrease in the number of acid-fast bacilli, which with increasing time stained less intensely and became more granular. Fibrin appeared still later and the acid-fast bacilli finally disappeared.

*Koch phenomenon:* The possibility that some of the tuberculin-negative cases had undergone a tuberculous infection during the time elapsing between the tuberculin test and the administration of the vaccine, or were in a pre-allergic state at the time of the tuberculin test, had to be given consideration. To check this possibility the site of injection of all BCG vaccinated cases was re-examined forty-eight hours after the vaccine was given to determine whether there was present an acute local inflammatory reaction (Koch phenomenon). In all there were observed 7 cases showing such an acute reaction. In 5 instances this was due to injection by error of tuberculin-positive cases, while in 2 instances the individuals had been tuberculin-negative at the time of testing but were evidently in a pre-allergic state at that time. It is of interest that these 2 cases have since died from tuberculosis and are included among the 6 deaths which occurred among the vaccinated in the course of this study.

*Roentgenologic Examinations:* Of the 3,008 persons included in this program, approximately 85 per cent were examined roentgenologically at the same time that the initial tuberculin test was carried out, or as soon thereafter as possible.

Re-examination of the BCG vaccinated and control groups was carried out at approximately annual intervals, and as many of the persons as could be located were tuberculin tested and examined roentgenologically. If they were absent from the Agency, efforts were made to determine their whereabouts and whether they were alive or dead.

#### EVALUATION OF RESULTS

An evaluation of the effectiveness of BCG vaccine cannot be made by comparing current mortality and morbidity rates from tuberculosis with former rates. Such a comparison is not valid principally because there has been a falling rate from tuberculosis for many years. The significance of the results obtained in this study depends upon the similarity of the vaccinated and control groups; the comparability of the per cent re-examined annually; and whether or not both groups experienced the same risk of exposure to tuberculous infection. The comparability of both groups in age distribution and sex has been presented in

table 4. The number re-examined annually by means of the tuberculin test and roentgenograms represents a high percentage of those in the study and, as indicated in table 5, is almost identical for both groups in any given year. The reduction and variations in the number re-examined after the sixth year are due to disruption of the study by World War II. In June 1944, field work was temporarily discontinued and at that time all of those in the study had had a minimum of six annual examinations. In some areas seven annual examinations had been made and in one Agency eight examinations had been carried out. In September 1946, field work was resumed and all of the areas were visited during 1946-47. At that time the tuberculin test and roentgenological examinations were made in some areas for the ninth year after the initiation of the study and for the tenth and eleventh years in the remaining areas. Consequently,

TABLE 5  
*Percentage of living persons in study re-examined annually*

| YEARS AFTER<br>VACCINATION | TUBERCULIN TESTED  |                      |                    |                      | X-RAYED            |                     |                    |                     |
|----------------------------|--------------------|----------------------|--------------------|----------------------|--------------------|---------------------|--------------------|---------------------|
|                            | Vaccinated         |                      | Control            |                      | Vaccinated         |                     | Control            |                     |
|                            | Original<br>number | Per cent<br>retested | Original<br>number | Per cent<br>retested | Original<br>number | Per cent<br>X-rayed | Original<br>number | Per cent<br>X-rayed |
| 1                          | 1,551              | 96.4                 | 1,457              | 90.4                 | 1,551              | 97.4                | 1,457              | 96.8                |
| 2                          | 1,551              | 94.5                 | 1,457              | 93.7                 | 1,551              | 96.8                | 1,457              | 96.4                |
| 3                          | 1,551              | 94.9                 | 1,457              | 95.4                 | 1,551              | 96.1                | 1,457              | 96.5                |
| 4                          | 1,551              | 95.2                 | 1,457              | 92.9                 | 1,551              | 95.9                | 1,457              | 93.9                |
| 5                          | 1,551              | 89.7                 | 1,457              | 90.0                 | 1,551              | 91.2                | 1,457              | 91.5                |
| 6                          | 1,551              | 80.8                 | 1,457              | 77.5                 | 1,551              | 84.1                | 1,457              | 81.8                |
| 7                          | 752                | 78.8                 | 702                | 81.6                 | 752                | 81.8                | 702                | 84.1                |
| 8                          | 428                | 70.4                 | 425                | 70.4                 | 428                | 71.6                | 425                | 76.3                |
| 9                          | 799                | 74.9                 | 755                | 72.1                 | 799                | 76.8                | 755                | 72.2                |
| 10                         | 266                | 68.6                 | 248                | 72.1                 | 266                | 69.0                | 248                | 72.1                |
| 11                         | 486                | 81.3                 | 454                | 78.3                 | 486                | 80.2                | 454                | 78.2                |

the per cent of persons re-examined following the sixth annual examination is based on the original number of cases in the areas visited and not on the original total of persons of all areas.

*Exposure to tuberculous infection:* An evaluation of the effectiveness of BCG vaccine in controlling tuberculosis can be made only if both groups experience the same risk of exposure to tuberculous infection. An analysis of the records of the first six years of this study under the direction of Dr. Carroll E. Palmer, Tuberculosis Control Division of the United States Public Health Service (60), showed that approximately 20 per cent of both groups was exposed to tuberculous infection and that the degree of contact was essentially the same for both groups. These results were based on known domiciliary sources of infection. There are, however, numerous extradomiciliary sources of infection which, while incalculable, are nevertheless significant. Thus bedridden tuberculous patients may be visited by large numbers of neighbors and friends, and tuberculous patients

who have left the sanatorium against advice attend public gatherings and visit friends and relatives and adjacent communities.

### *Development of Sensitivity to Tuberculin*

It cannot be said, at this time, that resistance to tuberculous infection is calculable by serological tests or degree of sensitivity to tuberculin. The writer has attempted in the past to correlate the development of specific antibodies and sensitivity to tuberculin with resistance to tuberculous reinfection. Goats and sheep were inoculated intrabronchially through a bronchoscope with increasing amounts of a viable, virulent bovine type tubercle bacillus. The development of specific antibodies was studied at frequent intervals over a period of two years by means of the precipitin reaction, agglutination, and complement

TABLE 6

*Frequency of tuberculin reaction by dose and year of observation in vaccinated and controls*

| YEARS AFTER<br>VACCINATION | VACCINATED         |                          |           |       | CONTROLS           |                          |           |       |
|----------------------------|--------------------|--------------------------|-----------|-------|--------------------|--------------------------|-----------|-------|
|                            | Original<br>number | Per cent positive to PPD |           |       | Original<br>number | Per cent positive to PPD |           |       |
|                            |                    | 0.00002 mg.              | 0.005 mg. | Total |                    | 0.00002 mg.              | 0.005 mg. | Total |
| 1                          | 1,551              | 36.7                     | 56.6      | 93.3  | 1,457              | 7.3                      | 5.4       | 12.7  |
| 2                          | 1,551              | 47.6                     | 45.7      | 93.3  | 1,457              | 13.5                     | 5.1       | 18.6  |
| 3                          | 1,551              | 54.5                     | 38.0      | 92.5  | 1,457              | 17.5                     | 7.1       | 24.6  |
| 4                          | 1,551              | 53.3                     | 38.9      | 92.2  | 1,457              | 22.7                     | 7.6       | 30.3  |
| 5                          | 1,551              | 54.9                     | 36.8      | 91.7  | 1,457              | 27.9                     | 7.2       | 35.1  |
| 6                          | 1,551              | 61.2                     | 31.0      | 92.2  | 1,457              | 33.0                     | 9.3       | 42.3  |
| 7                          | 752                | 58.0                     | 36.9      | 94.9  | 702                | 26.8                     | 11.4      | 38.2  |
| 8                          | 428                | 54.0                     | 40.9      | 94.9  | 425                | 25.3                     | 14.7      | 40.0  |
| 9                          | 799                | 76.7                     | 15.6      | 92.3  | 755                | 52.0                     | 3.0       | 55.0  |
| 10                         | 266                | 61.7                     | 25.8      | 87.5  | 248                | 26.3                     | 11.7      | 38.0  |
| 11                         | 486                | 61.4                     | 28.8      | 90.2  | 454                | 35.5                     | 6.2       | 41.7  |

fixation. At the same time the sensitivity of these animals to varying amounts of Old Tuberculin injected into the skin was studied. These unpublished studies indicated that, although specific antibodies and a high degree of sensitivity to tuberculin developed, no correlation could be demonstrated between the antibody titer, tuberculin sensitivity, and resistance to reinfection, as measured by tuberculosis mortality.

It is generally agreed that there exists a close relationship between allergy and immunity, but there is some evidence, with which the writer is in accord, that the two conditions do not necessarily coexist. For want of a better index in the present study, allergy as indicated by the tuberculin reaction is arbitrarily employed as a measure of immunity.

A positive tuberculin reaction following the administration of BCG has been interpreted as evidence of the establishment of an initial or primary tuberculous focus. From the values presented in table 6, it is evident that BCG vaccine induces a high sensitivity to tuberculin which persists for many years. It will

be noted from table 6 that among the vaccinated a positive tuberculin reaction was present in 93.3 per cent of those tested one year after vaccination and that this high rate has persisted with but slight variations through the period of observation. Among the control group, only 12.7 per cent reacted to tuberculin one year after the initial negative tuberculin reaction, and the increment of positive reactions was approximately 5 per cent per year for each subsequent year of observation.

The sensitivity to tuberculin induced by the intracutaneous administration of BCG vaccine is not as marked as that resulting from natural infection. This is indicated by the smaller per cent of the vaccinated who reacted to the initial dose of 0.00002 mg. of PPD and the less severe local reaction in the vaccinated than was noted in the controls who reacted. With increasing time the intensity of the tuberculin reaction also increased among the vaccinated. This suggests that among the vaccinated, as among the controls, natural infection with virulent tubercle bacilli had occurred.

### *Tuberculosis Morbidity*

Despite the fact that the interpretation of roentgenograms cannot as yet be considered entirely objective in nature, the procedure does offer the best medium for determining the presence and nature of pulmonary lesions. Unfortunately at this time an appreciable number of roentgenographs from the 1946-47 examination remain which show pulmonary lesions which have not as yet been definitely diagnosed. Pending a future review of the serial films of all cases with pathology of doubtful nature, the lesions will be reported tentatively as lesions of doubtful etiology. Figures on the occurrence of pulmonary lesions and deaths from tuberculosis according to the type or stage of the disease are presented in table 7 and graphically in figure 1.

It may be seen (table 7 and figure 1) that, with the exception of pleural effusion and pleural thickening, lesions showing the roentgenological characteristics of tuberculosis are significantly more frequent among the controls than among the vaccinated.

The determination of the cause of death was based on roentgenographic evidence in the case of pulmonary and bone and joint involvement, and on laboratory findings in cases of miliary tuberculosis and tuberculous peritonitis. As the examination of the roentgenograms was made without any prior knowledge of the tuberculin reaction and whether or not the film represented a vaccinated or control case, it was of interest to determine the relationship between the tuberculin reaction and the type of lesions found. The significance of the positive tuberculin reaction among the BCG vaccinated cases is marked by the large per cent of these who became tuberculin positive following vaccination. The change from a low degree of sensitivity to tuberculin to a high one, however, strongly suggests a tuberculous reinfection. In table 8 the relationship of the type of lesions to the tuberculin reaction is presented. In this table are presented, not only those who reacted to 0.00002 mg. or 0.005 mg. PPD, but those whose reaction has fluctuated from a high to a low or a low to a high level of

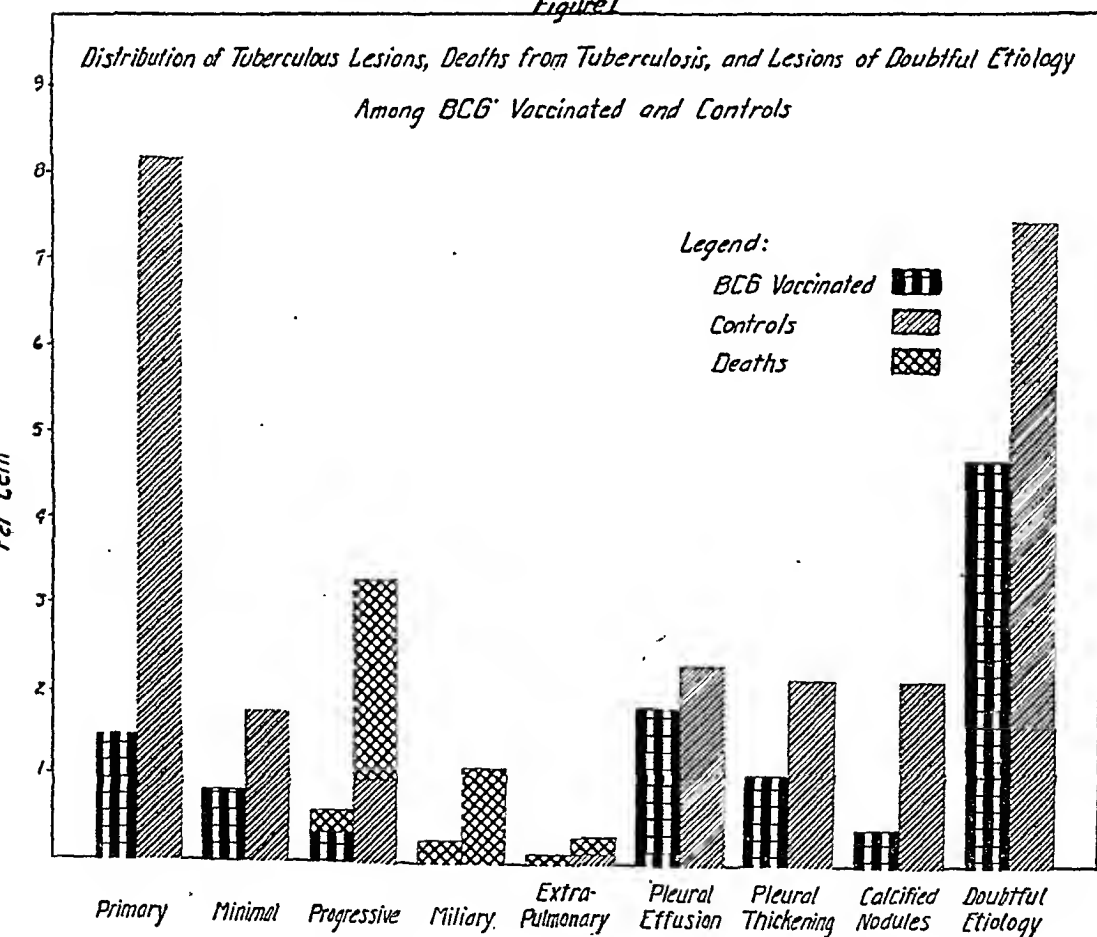
TABLE 7

*Occurrence of cases of tuberculosis and deaths according to lesion*

| TYPE OF LESION                | BCG VACCINATED |          |                  | CONTROLS |          |                  |
|-------------------------------|----------------|----------|------------------|----------|----------|------------------|
|                               | Number         | Per cent | Number of deaths | Number   | Per cent | Number of deaths |
| Primary.....                  | 22             | 1.4      | 0                | 120      | 8.2      | 0                |
| Minimal reinfection type..... | 10             | 0.6      | 0                | 25       | 1.7      | 0                |
| Progressive.....              | 8              | 0.5      | 3                | 49       | 3.3      | 34               |
| Miliary.....                  | 2              | 0.1      | 2                | 15       | 1.0      | 15               |
| Extrapulmonary.....           | 1              | 0.06     | 1                | 4        | 0.3      | 4                |
| Pleural effusion.....         | 27             | 1.7      | 0                | 33       | 2.2      | 0                |
| Pleural thickening.....       | 31             | 1.9      | 0                | 32       | 2.1      | 0                |
| Calcified nodule.....         | 6              | 0.4      | 0                | 31       | 2.1      | 0                |
| Doubtful etiology.....        | 75             | 4.8      | 0                | 114      | 7.8      | 0                |
| Total.....                    | 182            | 11.7     | 6                | 423      | 29.0     | 53               |

*Figure 1*

*Distribution of Tuberculous Lesions, Deaths from Tuberculosis, and Lesions of Doubtful Etiology  
Among BCG Vaccinated and Controls*





sensitivity, those whose tuberculin reaction has reverted from positive to negative, and those who have failed to react to tuberculin.

It will be noted that in the vast majority of cases, both among the vaccinated and among the controls, the presence of a lesion is associated with a high sensitivity to tuberculin. A low sensitivity to tuberculin, fluctuations in sensitivity,

TABLE 8  
*Relation of tuberculin reaction to type of lesion*

| TYPE OF LESION            | NUM-<br>BER OF<br>LE-<br>SIONS | POSITIVE<br>TO 0.00002<br>MG. PPD |             | POSITIVE<br>TO 0.005 MG.<br>PPD |             | FLUCTUATING<br>0.00002 MG.-<br>0.005 MG. PPD |             | POSITIVE<br>TO NEGATIVE<br>REACTION |             | NEGATIVE<br>TO 0.005 MG.<br>PPD |             |
|---------------------------|--------------------------------|-----------------------------------|-------------|---------------------------------|-------------|--|-------------|-------------------------------------|-------------|---------------------------------|-------------|
|                           |                                | Num-<br>ber                       | Per<br>cent | Num-<br>ber                     | Per<br>cent | Num-<br>ber                                  | Per<br>cent | Num-<br>ber                         | Per<br>cent | Num-<br>ber                     | Per<br>cent |
| In BCG vaccinated cases   |                                |                                   |             |                                 |             |  |             |                                     |             |                                 |             |
| Primary.....              | 22                             | 20                                | 90.9        | 1                               | 4.5         | 1  | 4.5         | 0                                   | —           | 0                               | —           |
| Minimal reinfection type. | 10                             | 9                                 | 90.0        | 0                               | —           | 1  | 10.0        | 0                                   | —           | 0                               | —           |
| Progressive.....          | 8                              | 8                                 | 100.0       | 0                               | —           | 0  | —           | 0                                   | —           | 0                               | —           |
| Miliary.....              | 2                              | 2*                                | 50.0        | 0                               | —           | 0  | —           | 0                                   | —           | 0                               | —           |
| Extrapulmonary.....       | 1                              | 1                                 | 100.0       | 0                               | —           | 0  | —           | 0                                   | —           | 0                               | —           |
| Pleural effusion.....     | 27                             | 25                                | 92.6        | 1                               | 3.7         | 0  | —           | 0                                   | —           | 1                               | 3.7         |
| Pleural thickening.....   | 31                             | 15                                | 48.4        | 9                               | 29.0        | 7  | 22.6        | 0                                   | —           | 0                               | —           |
| Calcified nodule.....     | 6                              | 6                                 | 100.0       | 0                               | —           | 0  | —           | 0                                   | —           | 0                               | —           |
| Doubtful etiology.....    | 75                             | 53                                | 70.6        | 7                               | 9.3         | 14   | 18.7        | 1                                   | 1.4         | 0                               | —           |
| Total.....                | 182                            | 139                               | 76.4        | 18                              | 9.9         | 23   | 12.6        | 1                                   | 0.5         | 1                               | 0.5         |
| In controls               |                                |                                   |             |                                 |             |  |             |                                     |             |                                 |             |
| Primary.....              | 120                            | 119                               | 99.1        | 0                               | —           | 0  | —           | 1                                   | 0.9         | 0                               | —           |
| Minimal reinfection type. | 25                             | 23                                | 92.0        | 0                               | —           | 1  | 4.0         | 0                                   | —           | 1                               | 4.0         |
| Progressive.....          | 49                             | 41                                | 83.7        | 0                               | —           | 0  | —           | 0                                   | —           | 8†                              | 16.3        |
| Miliary.....              | 15                             | 8                                 | 53.3        | 0                               | —           | 0  | —           | 0                                   | —           | 7†                              | 46.7        |
| Extrapulmonary.....       | 4                              | 3                                 | 75.0        | 0                               | —           | 0  | —           | 0                                   | —           | 1†                              | 25.0        |
| Pleural effusion.....     | 33                             | 24                                | 72.7        | 1                               | 3.1         | 0  | —           | 0                                   | —           | 8                               | 24.2        |
| Pleural thickening.....   | 32                             | 18                                | 56.3        | 2                               | 6.3         | 1  | 3.1         | 1                                   | 3.1         | 10                              | 31.2        |
| Calcified nodule.....     | 31                             | 29                                | 93.5        | 0                               | —           | 0  | —           | 0                                   | —           | 2                               | 6.4         |
| Doubtful etiology.....    | 114                            | 82                                | 71.9        | 0                               | —           | 1  | 0.9         | 4                                   | 3.5         | 27                              | 23.7        |
| Total.....                | 423                            | 347                               | 82.0        | 3                               | 0.7         | 3  | 0.7         | 6                                   | 1.4         | 64                              | 15.1        |

\* One showed Koch phenomenon on vaccination.

† Negative on last previous tuberculin test.

and failure to react to tuberculin, occur most frequently with pleural effusions and pleural thickenings which are probably nontuberculous in etiology.

Of the 53 deaths from tuberculosis among the controls during the course of the study, 23 occurred in persons who had their first positive tuberculin reaction one to seven years previously and had maintained their tuberculin sensitivity until time of death. Thirteen cases had a positive tuberculin reaction for the first time less than a year before death. Five persons had not been tuberculin tested within a year, but had failed to react to tuberculin the preceding year. One

case was tuberculin negative five months before death from tuberculous meningitis. A group of 11 had not been tested within the year of death, but their most recent tuberculin tests, two to four years previously, had been negative.

### *Tuberculosis Mortality*

The most striking evidence of the efficacy of BCG vaccine is brought out when the total mortality rates and the mortality rates from tuberculosis are compared in the vaccinated and control groups. Among the 1,551 vaccinated, a total of 55 persons died from all causes during the nine to eleven year period of this study. During this same period of time, 109 of the 1,457 controls have died from all causes. The BCG vaccinated group experienced a total of 16,406 person-years of observation, and in terms of deaths per 1,000 person-years yielded a rate of 3.1. The control group experienced a total of 15,207 person-years of

TABLE 9

*Mortality rates, tuberculous and nontuberculous, in vaccinated and controls by age groups*

| AGE<br>IN 5-YEAR<br>PERIODS | VACCINATED   |                          |                                       |                        |                                       | CONTROLS   |                          |                                       |                        |                                       |
|-----------------------------|--|--------------------------|---------------------------------------|------------------------|---------------------------------------|--|--------------------------|---------------------------------------|------------------------|---------------------------------------|
|                             | Number of<br>person-<br>years of<br>observa-<br>tion | Deaths—Tubercu-<br>losis |                                       | Deaths—Other<br>causes |                                       | Number of<br>person-<br>years of<br>observa-<br>tion | Deaths—Tubercu-<br>losis |                                       | Deaths—Other<br>causes |                                       |
|                             |  | Num-<br>ber              | Rate per<br>1,000<br>person-<br>years | Num-<br>ber            | Rate per<br>1,000<br>person-<br>years |  | Num-<br>ber              | Rate per<br>1,000<br>person-<br>years | Num-<br>ber            | Rate per<br>1,000<br>person-<br>years |
| 0 to 4                      | 1,327  | 1                        | 0.7                                   | 11                     | 8.3                                   | 1,303  | 2                        | 1.5                                   | 11                     | 8.4                                   |
| 5 to 9                      | 4,037  | 0                        | —                                     | 7                      | 1.7                                   | 3,757  | 6                        | 1.6                                   | 12                     | 3.2                                   |
| 10 to 14                    | 5,595  | 4                        | 0.7                                   | 9                      | 1.6                                   | 5,170  | 13                       | 2.5                                   | 9                      | 1.7                                   |
| 15 to 19                    | 3,998  | 1                        | 0.3                                   | 14                     | 3.5                                   | 3,667  | 22                       | 6.0                                   | 13                     | 3.6                                   |
| 20 to 24                    | 1,311  | 0                        | —                                     | 7                      | 5.3                                   | 1,179  | 10                       | 8.5                                   | 9                      | 8.1                                   |
| 25 to 29                    | 138  | 0                        | —                                     | 1                      | 7.3                                   | 131  | 0                        | —                                     | 2                      | 15.3                                  |
| Total.                      | 16,406   | 6                        | 0.4                                   | 49                     | 3.0                                   | 15,207   | 53                       | 3.5                                   | 56                     | 3.7                                   |

observation, and the rate per 1,000 person-years of observation was 7.2. These rates, when compared with the rates of 3.8 and 7.2 per 1,000 person-years for the vaccinated and control groups, respectively, noted at the end of the first six years of observation (58), indicate that the ratio of deaths in the two groups has remained almost constant. When death rate from tuberculosis is compared in the two groups, the difference is even more striking. In the BCG vaccinated group, 6 have died from tuberculosis since the beginning of the study, while among the controls 53 have died from this disease. The mortality rate from tuberculosis per 1,000 person-years of observation is 0.4 for the vaccinated and 3.5 for the controls. Of the 6 deaths from tuberculosis which occurred among the vaccinated, 2 were in persons who had a Koch phenomenon immediately after vaccination, while a third death occurred in a child who failed to react to tuberculin one year after vaccination.

In table 9 is presented a comparison of the mortality from tuberculosis and from other causes by five-year age periods.

This study has afforded an opportunity to determine the influence of age and sex on the occurrence of fatal tuberculosis in a population free from this disease at the initiation of the investigation. The number of deaths among the vaccinated is too small to permit conclusions on this basis. Among the control group, however, the number of deaths from tuberculosis is significant in each

TABLE 10

*Mortality rates, tuberculous and nontuberculous, by sex and age group among controls*

| AGE<br>IN 5-YEAR<br>PERIODS | MALE   |                          |                                       |                        |                                       | FEMALE   |                          |                                       |                        |                                       |
|-----------------------------|--|--------------------------|---------------------------------------|------------------------|---------------------------------------|--|--------------------------|---------------------------------------|------------------------|---------------------------------------|
|                             | Number of<br>person-<br>years of<br>observa-<br>tion | Deaths—Tubercu-<br>losis |                                       | Deaths—Other<br>causes |                                       | Number of<br>person-<br>years of<br>observa-<br>tion | Deaths—Tubercu-<br>losis |                                       | Deaths—Other<br>causes |                                       |
|                             |  | Num-<br>ber              | Rate per<br>1,000<br>person-<br>years | Num-<br>ber            | Rate per<br>1,000<br>person-<br>years |  | Num-<br>ber              | Rate per<br>1,000<br>person-<br>years | Num-<br>ber            | Rate per<br>1,000<br>person-<br>years |
| 0 to 4                      | 684  | 2                        | 2.9                                   | 4                      | 5.8                                   | 619  | 0                        | —                                     | 7                      | 11.6                                  |
| 5 to 9                      | 1,946  | 2                        | 1.0                                   | 8                      | 4.1                                   | 1,811  | 4                        | 2.2                                   | 4                      | 2.2                                   |
| 10 to 14                    | 2,694  | 2                        | 0.8                                   | 5                      | 1.9                                   | 2,491  | 11                       | 4.4                                   | 4                      | 1.6                                   |
| 15 to 19                    | 1,855  | 8                        | 4.3                                   | 6                      | 3.2                                   | 1,812  | 14                       | 7.7                                   | 7                      | 3.8                                   |
| 20 to 24                    | 559  | 5                        | 8.9                                   | 6                      | 10.7                                  | 624  | 5                        | 8.0                                   | 3                      | 4.8                                   |
| 25 to 29                    | 64   | 0                        | —                                     | 0                      | —                                     | 67   | 0                        | —                                     | 2                      | 30.0                                  |
| Total.                      | 7,702  | 19                       | 2.5                                   | 29                     | 3.8                                   | 7,424  | 34                       | 4.6                                   | 27                     | 3.7                                   |

TABLE 11

*Number and per cent of most frequent causes of death in BCG vaccinated and controls*

| DIAGNOSIS                   | VACCINATED |          | CONTROLS |          |
|-----------------------------|------------|----------|----------|----------|
|                             | Number     | Per cent | Number   | Per cent |
| Tuberculosis, all forms     | 6          | 0.38     | 53       | 3.63     |
| Accidents                   | 17         | 1.10     | 21       | 1.44     |
| Pneumonia, lobar            | 5          | 0.32     | 5        | 0.34     |
| Pneumonia, bronchial        | 5          | 0.32     | 3        | 0.20     |
| Peritonitis, acute          | 2          | 0.13     | 3        | 0.20     |
| Meningitis (nontuberculous) | 3          | 0.19     | 1        | 0.06     |
| Endocarditis                | 5          | 0.32     | 8        | 0.54     |
| Encephalitis                | 0          | —        | 2        | 0.13     |
| Postoperative               | 0          | —        | 2        | 0.13     |

five-year age period except for the 25 to 29 year group. In this group, the number of person-years of observation is too small for statistical analysis. It may be seen in table 10 that the mortality rate from tuberculosis rises sharply in the age groups 15 to 19 and 20 to 24, and that fatal tuberculosis occurs almost twice as often among the females as among the males. It is of interest that of the 6 who died from tuberculosis in the vaccinated group 4 were females and 2 were males.

The continued observation of a population of 3,008 persons predominately

of school age living in rural communities offered the unique opportunity of determining the most common causes of death. Among the vaccinated, a total of 55 persons died from all causes while, among the controls, 109 died. The reports of cause of death were based on the clinical records, nurses' notes, and death certificates. In addition to the most frequent causes of death presented in table 11 one each of the vaccinated died from the following causes: poliomyelitis, septicemia, dysentery, convulsions, diabetes mellitus, brain abscess, agranulocytosis, ruptured ectopic pregnancy, acute nephritis, uremia, embolism postpartum, and one cause unknown. Among the controls in addition to those presented in table 11 one each died from the following causes: dysentery, embolism postpartum, marasmus, typhoid fever, diphtheria, hemolytic anemia, acute alcoholism, acute adenitis, respiratory failure, mesenteric embolism, and one cause unknown.

One of the most impressive findings in this analysis is the large per cent of children who die from drowning, fire, automobile accidents and shooting. A number of deaths included in accidental deaths are those who were killed while serving in the armed forces in World War II. The homogeneity of the vaccinated and control groups is further indicated by the fact that deaths from non-tuberculous causes are in close agreement in both groups.

#### *Effectiveness of BCG Vaccine among Newborn Infants*

Because of the relatively high mortality from tuberculosis during the first three years of life, it was believed that a more rapid determination of the effectiveness of BCG vaccine in controlling tuberculosis could be made by observing a group of newborn infants for approximately five years. This supplementary study was carried out on infants born in the hospitals of the Turtle Mountain Agency, North Dakota, and the Rosebud Agency, South Dakota. The original plan was to vaccinate alternate cases in each hospital. Unfortunately this plan was not followed in one of the hospitals, and the newborn children were vaccinated there at random. Between December 1938 and December 1940, 123 newborn babies were vaccinated intracutaneously with 0.1 mg. of BCG vaccine within several days after birth. During the same period of time, 139 newborn babies were untreated and served as controls. The newborn babies returned home with their mothers and no change whatsoever was made in the home surroundings or mode of living. These babies, like those in the original study, were tuberculin tested and examined roentgenologically annually except for an interval during the war years. At the time of their first examination these children ranged in age from 3 to 14 months. At that time 85 per cent of the vaccinated and 77 per cent of the control group were tuberculin tested, and 95 per cent of both groups were examined roentgenologically. An analysis of the tests indicated that 91 per cent of the vaccinated and 3.7 per cent of the controls reacted to tuberculin. One case of primary tuberculosis was found in a control case at the first annual examination. This child died one month later from tuberculous meningitis. In 1946, when this "newborn" group ranged in age from 6 to 8 years, 82 per cent of each group were retested with tuberculin, while 83

per cent of the vaccinated and 78 per cent of the controls were examined roentgenologically. Among the vaccinated the tuberculin test was positive in 80 per cent of those tested, a decrease of 11 per cent from the results of tuberculin testing one year after vaccination. Among the controls, positive reaction to tuberculin had increased from the 3.7 per cent noted during the first year of life to 26.5 per cent.

During the six to eight years of observation, primary tuberculosis was found on roentgenological examination in 4 of the 123 vaccinated children and in 11 of the 139 controls. Of the 7 deaths among the vaccinated cases, none has been from tuberculosis, while, of the 15 deaths among the controls, 4 were due to tuberculosis. These 4 deaths all occurred within the first three years of life.

#### DISCUSSION

The accumulated data, both experimental and clinical, indicate that an initial infection with viable virulent or attenuated tubercle bacilli induces increased resistance to reinfection with virulent bacilli. There is, therefore, a sound basis for the use of the attenuated viable BCG strain of tubercle bacillus as an immunizing agent.

Although BCG vaccine has been used in man for the past twenty-five years, it has not received universal acceptance. The earliest objection to its use was the fear that the culture was not a virus fixé, as claimed by Calmette, and that it might regain its virulence. Petroff (61) claimed that the BCG strain could be dissociated into R and S variants and that the S variant was virulent for guinea pigs. These findings of Petroff have not been confirmed by other investigators. The innocuousness of the BCG vaccine for man is proved by the fact that, of the millions of persons who have received the vaccine, not a single unequivocal case of tuberculosis can be attributed to its use. In an animal as sensitive as the guinea pig, the writer has routinely injected from 10 to 20 mg. of different lots of BCG vaccine without any evidence of progressive tuberculosis.

The evidence has not been so clear cut as to the effectiveness of the BCG vaccine in controlling tuberculosis. This, in part, is due to the difficulties inherent in any attempt to carry out a long experiment in man under controlled conditions. Such a study requires that the number be sufficiently large to permit a statistical approach; that the treated and control groups be comparable in sex, age, economic level, and risk of exposure to tuberculous infection; that both groups be given the same medical care and follow up; that the morbidity and mortality be verified by roentgenological and laboratory procedures; and, finally, that both groups be followed for a long period of time. Needless to say it is difficult, if not impossible, to meet all of these criteria. An evaluation of the effectiveness of BCG vaccine on the basis of a reduction of the disease as compared with previous years is not valid since for many years there has been a steady decline of tuberculosis.

Although there has been a widespread use of BCG vaccine in man in some of the countries of Continental Europe, the Scandinavian countries, the countries of South America and in Japan, these programs were not carried out under the controlled conditions outlined above. Nevertheless, there is a considerable

body of circumstantial evidence that the use of the vaccine has reduced the morbidity and mortality from tuberculosis.

The most recent objection to the widespread use of BCG vaccine is based on the premise that the tuberculin reaction following the use of BCG vaccine would mask the tuberculin reaction resulting from spontaneous infection, thus making it more difficult to detect the sources of tuberculous infection. There is something to be said for this point of view and the objection might be given more serious consideration if the occurrence of tuberculosis in man approached the low rate now found among cattle in the United States. It cannot be given serious consideration, however, in existing areas in the United States with a mortality from tuberculosis of 300 and more per 100,000 population.

As to the advisability of the universal use of BCG vaccine, there is room for a difference of opinion. Certainly in those areas where the morbidity and mortality from tuberculosis are high, living conditions poor, and hospital facilities for the care of manifest cases of tuberculosis inadequate, the use of BCG vaccination is indicated. The use of BCG vaccine is definitely indicated in medical students, nurses, and other medical personnel who are tuberculin negative and who may be exposed frequently to tuberculous infection. For military personnel who are tuberculin negative and who are on duty in areas with a high incidence of tuberculosis, BCG vaccination should be carried out. Conversely, where the morbidity and mortality from tuberculosis are low and falling, where homes are widely scattered and housing and hospital facilities adequate, the universal use of BCG vaccine is debatable.

One of the immediate needs in the field of BCG vaccination is the establishment of uniform procedures for the administration and standardization of the vaccine. The question of setting up standards for potency and optimum dose remains to be solved, and methods of maintaining the viability of the bacterial suspension for a long period of time must be developed.

#### SUMMARY

1. The value of BCG vaccine in increasing resistance to tuberculous reinfection has been investigated under carefully controlled conditions among some Indians of the United States and Alaska.

2. Freshly prepared BCG vaccine was administered intracutaneously to 1,551 American Indians ranging in age from less than one year to 20 years and to 123 newborn infants. At the same time 1,457 Indians of comparable age and living under the same conditions received an intracutaneous injection of sterile physiological saline and served as controls. One hundred and thirty-nine newborn infants also served as controls.

3. No untoward local or general reaction followed the injection of the vaccine. In no instance did the regional lymph nodes ulcerate.

4. The original group of vaccinated and controls was followed over a period of nine to eleven years by means of tuberculin tests and roentgenograms of the chest, while the group of "newborn" infants was similarly followed for six to eight years.

5. The vaccinated cases were observed for a total of 16,406 person-years and

the controls for 15,207 person-years. The mortality rate from all causes was 3.1 per 1,000 person-years of observation for the vaccinated and 7.2 for the controls.

6. Among the 1,551 BCG vaccinated there occurred a total of 55 deaths, including 6 deaths from tuberculosis. Among the 1,457 controls there occurred a total of 109 deaths, including 53 deaths from tuberculosis. The mortality rate from tuberculosis per 1,000 person-years of observation was 0.4, and 3.5 for the vaccinated and controls, respectively.

7. Among the controls the death rate from tuberculosis was highest among the males in the 15 to 19 and 20 to 24 year age group, and in the females in the 10 to 14 and 15 to 19 age group. It was approximately twice as high among the females as among the males.

8. Among the 123 newborn infants, who were vaccinated and observed for six to eight years, 7 have died, none from tuberculosis. Among the 139 newborn controls, 15 have died, 4 of them from tuberculosis.

9. The tuberculin reaction became positive one year after vaccination in 93.3 per cent of cases and has remained at approximately the same level throughout the course of this study. Among the controls the tuberculin reaction became positive in 12.7 per cent within one year after the initial negative reaction, and there has been a constant and gradual increase in the per cent of the controls reacting to tuberculin.

10. Roentgenologically demonstrable lesions having the characteristics of primary tuberculosis occurred in 22 of the vaccinated and in 120 of the controls. Minimal lesions of reinfection type, progressive lesions and miliary and extrapulmonary lesions of tuberculosis were found in 21 of the vaccinated and in 93 of the controls.

#### SUMARIO

##### *Vacunación Antituberculosa con Referencia Particular a BCG*

1. El valor de la vacuna BCG para acrecentar la resistencia a la reinfección tuberculosa ha sido investigado, bajo condiciones euidadosamente comprobadas, en algunos indios de los Estados Unidos y Alaska.

2. A 1,551 indios, cuya edad variaba de menos de un año a 20 años, y a 123 recién nacidos se les administró intracutáneamente vacuna BCG recién preparada. Al mismo tiempo, 1,457 indios de edad comparable y viviendo en las mismas condiciones recibieron una inyección intracutánea de suero fisiológico y sirvieron de testigos. También se tomó como testigos a 139 recién nacidos.

3. La inyección de la vacuna no fué seguida de la menor reacción local o general contraproducente. En ningún caso supuraron los ganglios linfáticos regionales.

4. El primitivo grupo de vacunados y testigos fué pesquisado durante un período de nueve a once años por medio de reacciones a la tuberculina y radiografías torácicas, y el grupo de recién nacidos en forma semejante durante seis a ocho años.

5. Los casos vacunados fueron observados durante un total de 16,406 per-

sonas-años y los testigos durante 15,207 personas-años. La mortalidad por todas causas representó 3.1 por 1,000 personas-años de observación en los vacunados y 7.2 en los testigos.

6. Entre los 1,551 vacunados con BCG hubo un total de 55 muertes, comprendiendo 6 debidas a tuberculosis. Entre los 1,457 testigos hubo un total de 109 muertes, incluso 53 debidas a tuberculosis. La mortalidad tuberculosa ascendió a 0.4 y 3.5 en los vacunados y los testigos, respectivamente.

7. Entre los testigos la mortalidad tuberculosa alcanzó su máximo en los varones de los grupos de 15 a 19 y 20 a 24 años de edad, y en las mujeres en los grupos de 10 a 14 y 15 a 19 años, representando aproximadamente el doble entre las mujeres que entre los hombres.

8. Entre los 123 recién nacidos vacunados y observados durante seis a ocho años, 7 han muerto, ninguno de tuberculosis. Entre los 139 recién nacidos testigos, 15 han muerto, 4 de ellos de tuberculosis.

9. La reacción a la tuberculina viró a positiva al año de la vacunación en 93.3 por ciento de los casos y ha permanecido aproximadamente a la misma cifra durante todo este estudio. Entre los testigos, se volvió positiva en 12.7 por ciento en término de un año de la reacción negativa inicial, habiendo desde entonces un aumento constante y paulatino en el porcentaje de testigos que reaccionan a la tuberculina.

10. En 22 de los vacunados y en 120 de los testigos, presentáronse lesiones radiológicamente observables que mostraban las características de la tuberculosis primaria, en tanto que en 21 de los vacunados y 93 de los testigos descubriéronse lesiones mínimas de tipo reinfección, lesiones evolutivas y lesiones granúlicas y extrapulmonares de tuberculosis.

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# RECURRENCE OF COCCIDIOIDAL CAVITIES FOLLOWING LOBECTOMY FOR A BLEEDING FOCUS<sup>1</sup>

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## INTRODUCTION

Perusal of the literature and personal communication with several workers in the field reveal that lobectomy has been performed in a large number of patients with coccidioidomycosis, many of whom have not been reported. The indications have usually included: (1) failure of the cavity to close after a period of observation; (2) failure of pneumothorax to close such a cavity; and (3) inability to differentiate a round roentgenographic shadow of coccidioidal granuloma from that of peripheral carcinoma or tuberculoma. Recently, persistent hemorrhage has also been regarded as an indication for lobectomy, though to date only two cases have been mentioned in the literature (1, 2).

The purpose of this paper is to discuss briefly the dangers of coccidioidal cavities and to report the case of a patient with a bleeding coccidioidal cavity treated by lobectomy, who was seen one year later with recurrent coccidioidal cavities in the remaining lobe of his lung.

## Dangers of Coccidioidal Cavities

The inherent threats in coccidioidal cavity have been variously ascribed to: (1) contagion, (2) dissemination, and (3) severe hemorrhage.

Contagion is generally considered improbable. Inhalation of the chlamydospores of *coccidioides immitis* is the only recognized method of acquiring pulmonary coccidioidomycosis. The change undergone by the fungus in the human host results in the finding of endospores within the lesion, but chlamydospores are not ordinarily demonstrable. Thus, the disease has not heretofore been regarded as transmissible from person to person. In Barnes' discussion of a recent paper (1), however, reference is made to the finding of both chlamydospores and endospores in a coccidioidal cavity which was removed by lobectomy. More recently, Rosenthal and Routien (3) have published results of experiments with guinea pigs in which material from human hosts was proven to be contagious, man to animal and animal to animal. These findings stimulate reconsideration of the problem of contagion, which merits further investigation.

Dissemination of the fungus in the absence of early walling off of the pulmonary lesion is a recognized possibility (4, 5). In 1942, Peers, Holman, and Smith described a case of solitary coccidioidal cavity in which lobectomy was performed because of the danger of spread from the "focalized" lesion throughout the rest of

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the body. Other papers have also indicated a high degree of resistance to reinfection inherent in the solitary coccidioid focus (6, 7, 8). Nevertheless, the recent studies of disseminated coccidioidomycosis by Forbus indicate that generalization from an established focus in the body may occur at any time in the course of the disease, even after as long a period as ten years (4).

Bleeding is a frequent occurrence, but its potential seriousness has seldom necessitated comment. Occasional hemoptysis is a common sign which disappears with spontaneous closure of the cavity. Rarely, the cavity may remain open and bleeding be repeated and severe. This condition may fail to respond to collapse therapy and thereby present a serious threat to normal existence. The present report illustrates this type of course and also reveals a previously unreported complication, *i.e.*, the lighting up of hidden foci of pulmonary coccidioid granulomata after removal of a solitary focus.

#### CASE REPORT

The patient, a 23-year-old white male, entered the Veterans Administration Hospital, Bronx, New York, August 4, 1946, complaining of repeated episodes of "coughing up blood." His initial symptoms began in March 1945, when, while performing calisthenics, he had a spontaneous hemoptysis productive of approximately one pint of bright red blood. Bleeding recurred the next day, and he was admitted to the Will Rogers Field Hospital, Oklahoma.

The patient had previously been in good health. In October 1942, he had enlisted in the A.A.F. and completed a year's basic training at various air fields located in the southwest (Amarillo, Texas; San Diego, California; Tucson, Arizona, and Albuquerque, New Mexico). He was sent to Italy in December 1943, and in fifteen months had flown on fifty air missions, followed by furlough to the United States. His health had been excellent throughout this entire period and, except for a mild frostbite of the feet, and scabies, he had had no significant illnesses.

Investigation for tuberculosis at Will Rogers Field Hospital was negative and the patient was transferred to the Fitzsimmons General Hospital, Denver, Colorado. There he was told he had coccidioidomycosis of the lung with a cavity in the right upper lobe. He was advised that the cavity would close and was discharged from the Army in June 1945.

From that time until his admission to the Veterans Hospital he had frequent bouts of hemoptysis, some of which amounted to as much as a pint, and by May, 1946, any moderate exertion was sufficient to excite a hemorrhage. The patient became apprehensive and nervous and was unable to pursue his normal occupation of truck-driving because of the constant threat of sudden copious hemoptysis.

In August 1946, after a severe bout of bleeding, he was referred to this hospital. He had lost 23 pounds in the preceding three months and had developed a dull ache at the right upper parasternal border.

*Physical Examination On Admission:* The patient was a tall, fairly well developed, white male in no apparent distress. Temperature was 99°F. and, aside from a mild pallor of the mucous membranes and skin, there were no abnormal physical findings.

*Laboratory Data:* The erythrocyte count varied from 3,000,000 to 4,000,000 per cu. mm. with 12 grams of hemoglobin. The total leucocyte count ranged from 11,000 to 5,200 per cu. mm. with 2 to 4 per cent eosinophils. The erythrocyte sedimentation rate (Cutler Method) ranged between 18 mm. to 9 mm. per hour. Urinalyses and serologic tests for

syphilis were negative. Examination of sputum and gastric washings revealed no tubercle bacilli. Cultures of the sputum and bronchial secretions were negative for *coccidioides immitis*. Intracutaneous tuberculin tests with PPD were negative. The coccidioidin skin test was positive in a 1:10 dilution on three separate occasions. The same antigen produced a marked skin reaction in another patient in a 1:1,000 dilution.

The first series of roentgenograms showed a lesion in the right apex, which was interpreted as minimal pulmonary tuberculosis. A cavity was not visualized in the conventional postero-anterior films. A subsequent film in the lordotic view, however, revealed a small, round, thin walled cavity in the right apex (figure 1).



FIG. 1. November 15, 1946. A lordotic view of the chest demonstrating the round, thin walled cavity in the right apex.

In the differential diagnosis, tuberculosis, coccidioidomycosis, and chronic abscess were considered. Failure to find tubercle bacilli in the sputum and the negative tuberculin tests were believed to exclude the possibility of tuberculosis, and the history was not suggestive of chronic abscess. Thus, partly by exclusion, and partly by virtue of a weakly positive coccidioidin test with history of residence in an endemic area, the clinical impression of coccidioidomycosis was felt to be reasonable. Actually, however, the inability to demonstrate the etiologic organism prevented a positive clinical diagnosis.

*Course:* Because of recurrent bleeding, a right pneumothorax was instituted, but failed to collapse the cavity-bearing area which was broadly adherent. Thoracoplasty was considered but was rejected, in view of the improbability of tuberculosis and the possibility of cavity epithelialization. It was felt that if a coccidioidal cavity or nonspecific chronic

abscess were present, lobectomy would remove the entire diseased area, including the source of bleeding. On November 20, 1946, lobectomy was performed by Dr. Elliott Michelson, assisted by Dr. Richmond L. Moore and Dr. Gustave A. Haggstrom.

*Operation:* At operation a large, thick, vascular adhesion, which bound the cavitory portion of the apex of the right upper lobe to the extreme cupola of the chest wall, was demonstrated. Except for this adhesion, the pleura was smooth and glistening and showed no evidence of disease. No fissure existed between the right upper and right middle lobes and it was found necessary to remove these two en masse. The operation was not technically difficult and the patient's condition was satisfactory throughout the procedure.

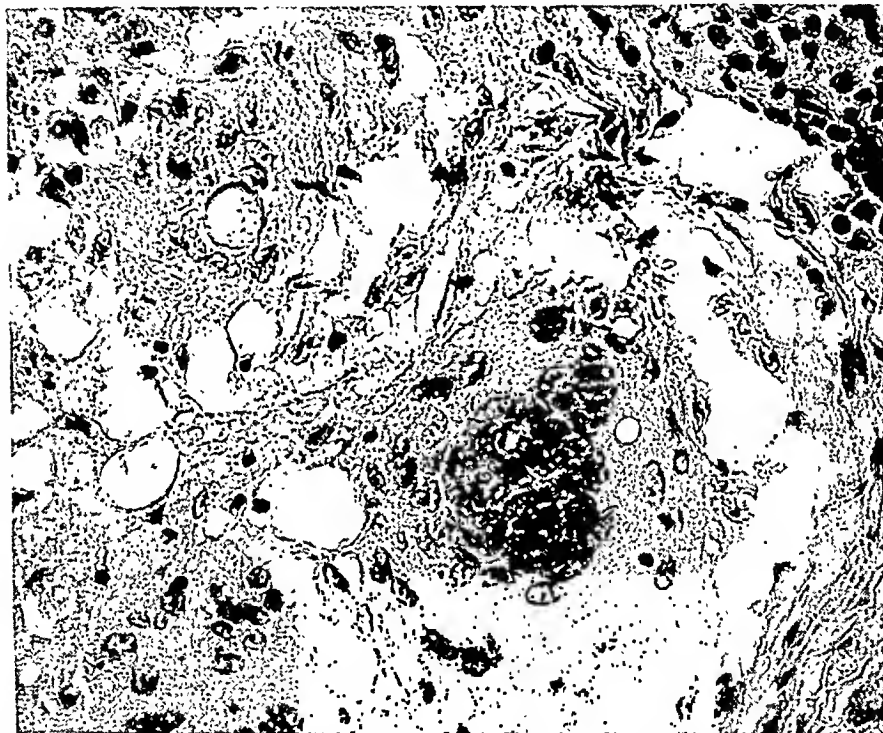


FIG. 2. Histologic section of pulmonary parenchyma showing giant cell containing doubly refractile body within which endospores of coccidioides immitis are visible ( $\times 430$ ).

*Histopathology:* The surgical specimen consisted of the right upper and middle lobes of the right upper bronchus. When sectioned and opened, the distal two-thirds were dilated and opened into a cavity 2.5 cm. in diameter. The cavity lining was rough and fibrotic and presented numerous irregularly shaped gray thickened patches extending into surrounding compressed parenchyma. Histologic section revealed tubercles composed of epithelioid cells scattered throughout the parenchyma surrounding the cavity and the proximal bronchus. Large giant cells (figure 2) were noted. Some of these cells contained doubly refractile bodies within which were seen endospores of coccidioides immitis. There was fibrous tissue around some tubercles containing many lymphocytes. A part of the bronchus showed marked hyalinization of the basement membrane with

inflammatory infiltrate present within the submucosa. Fibrosis was also noted in the wall with numerous eosinophil and lymphocytic infiltrations. The mucosal lining of the dilated bronchus was intact, though flattened and distorted, and the myoclastic layer was thinned and stretched. The section was interpreted by Dr. E. S. Olsen, pathologist, and reviewed by Dr. Fred Stewart, Consultant in Pathology, who concurred in the diagnosis of coccidioidomycosis.

*Postoperative Course:* The patient had a relatively uneventful postoperative course. He developed a moderate right hydropneumothorax, which quickly resorbed with subsequent expansion of the right lower lobe to fill the chest cage. By November 26, 1946, he was ambulant, and on December 14, 1946, he was discharged from the hospital, symptom free.

A follow-up examination on June 5, 1947, revealed that the patient had gained 17 pounds since discharge. He complained of occasional dyspnea, easy fatigue on exertion, occasional palpitation of the heart, and cough productive of a small amount (4 to 8 cc.) of gray white phlegm. There had been no recurrence of hemoptysis. Physical examination revealed a slight lag in expansion of the right hemithorax, diminished fremitus, and diminished breath sounds over the right posterior base. There were no cardiac abnormalities. Laboratory studies showed: an erythrocyte count of 4.73 million per cu. mm. with 16 grams of hemoglobin; a total leucocyte count of 6.8 thousand per cu. mm. with 66 per cent neutrophils, 32 per cent lymphocytes and 2 per cent monocytes; and an erythrocyte sedimentation rate of 6 mm. per hour (Cutler Method). Two sputum studies (performed in an outside laboratory) were reported negative for *coccidioides immitis*. The vital capacity was 3.6 liters (normal 5.0 liters). The electrocardiogram was normal and the chest roentgenogram revealed no evidence of active coccidioidal disease.

In November 1947, the patient returned to work, which consisted of moving 50 pound shingles for eight hours each day. Shortly thereafter, he noted the return of his cough and a gradual loss in weight. In December 1947, a low grade fever became apparent. His sputum increased to 180 cc. daily and was tinged with bright red blood.

*Readmission to hospital:* On admission to this hospital in January 1948, he was found to have lost 13 pounds since last seen (June 1947). There was a lag of the right hemithorax, and diminished breath sounds and fremitus in this area. A slight wheeze over the right apex was heard, but no rales or other adventitious sounds were present. The erythrocyte count was 4.5 million per cu. mm. with 15 grams of hemoglobin, and the total leucocyte count was 11,450 with 76 per cent neutrophils, 10 per cent eosinophils and 14 per cent lymphocytes. The erythrocyte sedimentation rate was 11 mm. per hour (Cutler Method). Examination of one sputum smear revealed a suspicious endospore, but eight cultures and guinea pig inoculations of the sputum failed to produce evidence of *coccidioides immitis* or tubercle bacilli. *Monilia albicans* was found in profusion. A skin test with coccidioidin was positive in a 1:10 dilution. The tuberculin test was negative. A complement fixation test for coccidioidomycosis (done through the courtesy of Dr. Charles E. Smith of Stanford University) was equivocal (2 plus in a 1:2 dilution). A precipitin test with the same antigen was also negative. Doctor Smith indicated that this was compatible with coccidioidal cavitation and, in view of the low titer of the complement fixation test, felt that the disease was not progressive or disseminating.

Serial roentgenograms and laminographs of the chest revealed a moderate amount of infiltration in the right upper lung field from the first to the seventh ribs, and three large thin walled annular cavities in the posterior segment of this lung (figure 3). There was calcification in both hilar areas. The left lung was free of disease. Urine cultures and

bone surveys revealed no evidence of disseminated coccidioidomycosis. Bronchoscopy showed no local disease in the bronchial tree. The right lower lobe, middle lobe and upper lobe orifices were all seen. The upper lobe orifice was occluded and slit-like. The middle lobe orifice was open. Whitish secretion was coming from the right lower lobe bronchus. The apical branch of the right lower lobe was not visualized.



Fig. 3. February 10, 1948. A postero-anterior view of the chest showing three thin walled annular cavities in the posterior segment of the right lung.

The patient had a low grade fever for several days and continued to cough up increasing amounts of bloody sputum. A one month trial period of strict bed-rest resulted in a normal temperature and blood count and the sputum decreased slightly in amount. The hemoptyses continued, however, and roentgenograms revealed no change in the size of the lung cavities.

It was felt that further excisional surgery was not indicated in this patient because of the possible systemic nature of the disease and the follow-up results of his lobectomy. From the long range view point, permanent collapse therapy, followed by a period of supervised rest, seemed advisable. On March 5, 1948, a first stage thoracoplasty (performed by Dr. Walter Wahrenberger and Dr. Paul Kirschner), with resection of the first



three ribs, was done, and on March 19th the fourth, fifth, sixth and seventh ribs were resected by Dr. Bernard J. Ryan and Dr. Paul Kirschner. A satisfactory collapse was obtained, and postoperative convalescence was uneventful.

#### COMMENT

The patient was in good health from the period of exposure in 1943 to March 1945, and fits into that group of patients who show no signs of disease prior to the first hemoptysis. His bleeding was persistent and incapacitating. It gave rise to a chronic anemia, afforded a constant threat to his well-being and mental security, and reduced his functional status to that of an invalid.

During the patient's first admission in August 1946, although it was never possible to isolate *coccidioides immitis*, and the skin tests were only weakly positive, it was felt that the history, clinical course, and roentgenographic appearance of the cavity were compatible with the diagnosis of coccidioidomycosis. On that admission, pneumothorax failed to collapse the cavity because of apical adhesions. Thoracoplasty was considered and, in retrospect, might have resulted in satisfactory closure of the cavity with eventual fibrosis by apposition of the granulating surfaces as in tuberculosis. In the hope of removing the disease focus completely, however, and hence preventing further bleeding, lobectomy was decided upon.

The reappearance of the patient's symptoms and the cavitation in the remaining lung lobe were doubtless influenced by the strenuous exertion demanded by his work, with the coincident overexpansion of the remaining lobe of the right lung. This is the first recorded instance, to the writer's knowledge, of the recurrence of coccidioidal cavities in the lung following lobectomy. Personal communication with Dr. Charles E. Smith of Stanford University reveals that patients who have undergone lobectomy for coccidioidal infection generally do well. Follow-up studies, however, have not previously been reported.

Usually the patient with a residual coccidioidal cavity does well on conservative therapy (9, 10, 11) and after several weeks or months the cavity gradually closes and heals, leaving a small residual scar. Surgery is rarely necessary. Pneumothorax, when tried, has occasionally resulted in tension cavities (1), and cases of persistent cavity, even after two years of pneumothorax, have been reported (5, 11). More recently, lobectomies have been done in increasing numbers. With the present case in mind, the decision in favor of lobectomy should be made with caution. Forbus has shown that small coccidioidal foci in the lung may lie dormant for years and then flare up with a resultant dissemination throughout the body (4). The present case illustrates this danger, although fortunately no evidence of dissemination or progressive disease was apparent in this patient. With the difficulty attendant on the detection of these small granulomatous lesions by roentgenogram (12) and the possibility of their reanimation, it seems plausible, in therapy, to stress the principle of enforced rest of the affected parts. It would seem that this can be most satisfactorily accomplished by thoracoplasty. Not only does permanent collapse prevent

undue expansion of the residual lobes, but it also favors the coaptation of the cavity walls and healing with scarring and fibrosis.

# SUMMARY

1. A brief discussion of the recognized indications for lobectomy and the inherent dangers in pulmonary coccidioidomycosis is presented.

2. A case is reported in which persistent hemoptysis from a coccidioidal cavity proved severe enough to warrant surgical resection of the involved lobe.

3. After a period of one year, the case was complicated by the appearance of coccidioidal cavities in the remaining lobe of the previously operated lung.

# SUMARIO

## *Recurrencia de Cavernas Coccidioideas después de una Lobectomía por Foco Hemorrágico*

1. En una breve reseña se repasan las indicaciones reconocidas de la lobectomía y los peligros que entraña en la coccidioidomicosis pulmonar.

2. Comunícase un caso en el cual la persistente hemoptisis procedente de una caverna coccidioidea resultó tan grave que justificó la resección quirúrgica del lóbulo afectado.

3. Al cabo de un año, complicó el caso la aparición de cavernas coccidioideas en el lóbulo restante del pulmón previamente operado.

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## THORACOPLASTY WITHOUT APICOLYSIS

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The modifications of thoracoplasty are still increasing in number. From this fact it is evident that the surgeons are not satisfied with the results obtained and there is a trend toward efforts to attain a higher percentage of restitution. In the writer's opinion, much better results can hardly be expected. The comparison of the results obtained by thoracoplasty and pneumothorax, respectively, show that the percentage of those patients cured by thoracoplasty is not lower than that of the patients cured by pneumothorax. The surgeons concerned with the collapse treatment of pulmonary tuberculosis have to be satisfied with the fact that restoration cannot be attained in more than 70 per cent of the cases, even if the patients to be operated are so carefully selected as to ensure a favorable prognosis. Operative mortality, disturbed wound healing and, particularly, the exacerbation of the process collapsed at operation are factors to be reckoned with. Every surgeon has had cases in which operation has been followed by restitution against expectation while other cases exhibiting an apparently good prognosis have been lost.

Sauerbruch intended only to loosen the lungs by his operation which, when performed properly, was followed by good results.

In contrast, Graf emphasized that only a complete collapse could bring about healing. He considered restoration following an incomplete collapse a fortuitous circumstance. Therefore, as early as 1930, he suggested a complete horizontal elimination of the apical area in order to bring about a thorough collapse. He performed widespread apicolyses, a method soon adopted by nearly all surgeons, though most of them suggested various modifications regarding apicolysis. Of these the modification initiated by Semb should be mentioned. This author has emphasized that the apex may, following apicolysis, dilate within the cavity left below the shoulder muscles and the scapula so that the success of the operation may be lessened or annihilated. Semb's procedure is doubtless the best, yet it has not been widely adopted, probably because the results obtained by other modifications are not perceptibly worse.

As in any other branch of surgery, the operative methods aiming at a cure for tuberculosis have the goal of attempting to bring about the best conditions of healing by means of the slightest intervention. The main object is invariably restoration. A simple operation, well tolerated by the patients, is not acceptable if its restoration percentage is low. For this reason, plombage or drainage of the cavity are operations of historical interest only and the instances suitable for extrapleural pneumothorax or oleothorax are rather infrequent.

The high number of ideas and suggested operations is by itself proof of the inadequacy of our knowledge of the essential features of the pulmonary processes and of the mechanical and dynamic factors prevailing in the thorax. It would

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be easy to select the most suitable operative procedure in a given case if these factors were precisely known.

No doubt, much progress has been made in this field since the epoch of the so-called type operations came to its end about 1930. The sequel of the new trend has been a mass of modifications among which the choice of the most suitable one was a difficult task even for a trained surgeon. Although "type operations" are superseded, every surgeon concerned with collapse therapy has chosen a method to be applied more or less routinely; the only variety being the adaptation of the procedure to the extension of the process. Thus, every surgeon aims at working out an operative procedure to be applied in all cases of pulmonary disease with a hope for success.

The writer had the opportunity to observe Graf's work. First, he advocated thoracoplasty, then extrapleural pneumothorax and oleothorax, and finally he returned to thoracoplasty because, in his opinion, the results of the extrapleural procedures had not been satisfactory. The technique of the thoracoplasty applied by him is similar to that based on the original idea of Sauerbruch. The enormous material treated by Graf (over 2,000 cases of extrapleural oleothorax) should have afforded an opportunity to find the most suitable form of collapse therapy on an experimental basis. In 1941, he told the writer that his method recently developed and termed "extraperiosteal thoracoplasty" seemed to be the most promising of all employed up to that time and that consequently he intended to use this method routinely. In the course of this operation, ribs are excised paravertebrally, together with the periosteum, in such a way that a 3 cm. piece of the first rib and 8 to 10 cm. of the other ribs are removed and the medial stumps are exarticulated. Two weeks later, a second stage is performed consisting of the removal of the cartilages of ribs one to four and, between the mamillar and anterior axillary line, a piece measuring 2 to 3 cm. each of the ribs two, three and four, together with their periosteum. No apicolysis is performed with the excision of the ribs. The operation results in an "excessive mobilization of the thorax" and yet fails to bring about an absolute collapse. Healing, including the closure of the cavity, would be executed by the shrinkage occurring within the thorax. The operation is virtually a kind of thoracoplasty applicable to various types of process, without regard to the size and situation of cavities. The development of Graf's views on collapse therapy, from originally advocating large-scale apicolysis to eventually omitting apicolysis, is an interesting process. As yet, the writer has had no opportunity to apply this method of Graf's though the results observed in his department were rather good.

Apicolysis has been omitted also by Maurer in his apicoplasty. The writer performs apicoplasty with Maurer's method, with the addition that the ribs are exarticulated in order to enhance collapse. The good results obtained by this procedure suggested that thoracoplasty without apicolysis might be advisable. This notion was strengthened by the observation that in those instances in which apicolysis could not be performed on account of widespread adhesions the results were no worse than when apicolysis was performed. Moreover, cases were observed in which the patient healed despite the fact that apicolysis was successful

on the lateral part only and the medially situated cavity remained distended. In other cases it sank into a "dead space" and, despite the repeated corrective operations performed later, could not be collapsed.

As mentioned above, the writer performs Maurer's apicoplasty in apical processes. The second stage is performed two weeks later from a similar paravertebral incision. The length of the costal pieces to be removed of the four upper ribs is calculated from the chest film as follows: If an alteration is present extending to the sixth rib, of the ribs superior to the border of alteration a section is removed, the initial point of which lies paravertebrally and the end point at the crossing with the sixth rib. In other words, the whole paravertebral part of the ribs superior to the border of the alteration (sixth rib) is removed. If the pathologic process has spread down below the fifth rib, the eighth rib thoracoplasty is the operation of choice. The latter is performed as a two stage operation from below upward. After a paravertebral block anaesthesia, a paravertebral incision is made, the lower half of which is directed slightly outward. After the muscles have been severed, the ribs to be excised (five, six, seven, and eight) are exposed. Their periosteum is incised and removed, then a paravertebral piece of them, measuring 14 to 15 cm., is excised subperiosteally and finally the medial stumps of the ribs are exarticulated. In the region of the excised ribs, their periosteal sheaths, the intercostal muscles, vessels, and nerves, are dissected off the pleura and removed except for the eighth intercostal nerve. As is commonly known, the intercostal nerves downward from the eighth supply trophic fibers to the abdominal muscles. Hence, they must be spared for otherwise the upper part of the abdominal muscles would undergo atrophy and herniation. Bleeding is controlled and the wound should heal by primary closure. The length of the rib parts to be removed can be estimated from the chest film. In a process extending to the sixth rib, the second rib is nearly totally excised, whereas in an alteration extending to the seventh rib the whole bony part of the rib should be removed. The medial stumps are exarticulated, the periosteum and the intercostal soft parts are left in place and primary closure is made.

There are several reasons why it is advisable to commence the operation at its lower point. Operation on the lower part is easier to perform and better tolerated by the patient as it causes no strain on the pulmonary circulation. The fact that costal respiration is abolished will not impair the total gas interchange. No paradoxical respiration ensues and the hazard of the operation consists in the shock. Moreover, the first stage may be considered a clinical-biological experiment which affords a reliable test for judging the general condition of the patient, the capacity of his circulation, and the reaction of the pulmonary process to the intervention. The time at which the second stage should be performed may be determined in accordance with the general condition of the patient for the costal regenerations developing in four to eight weeks do not interfere with the success of the second stage.

On a theoretical basis, which is supported by clinical observations as well, the interval between the two stages should be at least three weeks. This is the time needed for the mediastinum to become fastened at its upper part. Otherwise

excessive mobilization due to the second stage may result in mediastinal fibrillation or paradoxical respiration to such an extent as to form a serious danger for the patient.

The periosteum of the four upper ribs are left intact because here the chest wall may, especially on the side and in front, become too loose after the costal periosteum has been removed. This condition may frequently be observed after Graf's operation of mobilizing the anterior thorax wall. The periosteum of the lower ribs may safely be removed because this part is protected by the scapula. Exarticulation of the ribs is an additional factor in the collapse and the "dead space" lying by the vertebral column is thus reduced to a minimum.

The writer performs the ten rib thoracoplasty in a similar manner, apart from its division into three stages consisting of three, three, and four ribs, respectively. The four upper ribs are excised in the last stage. As in the eight rib thoracoplasty, the eighth intercostal nerve and the ninth and tenth nerves are spared. In a ten rib thoracoplasty, occasionally the third rib may be excised as far forward as the costochondral junction. Through the exarticulation of the ribs, after having resected the first rib totally and the second one subtotally, the collapse of the apex will be complete without apicolysis. Thus the complications of the apicolysis may be prevented and the final and simultaneously most difficult stage of the operation is abbreviated. The latter fact is relevant in the cases in which the general condition of the patient is unsatisfactory.

The ten rib thoracoplasty is performed like the eight rib operation, starting from below and completed in three stages. The interval between the single stages is likewise three weeks. In the first stage a piece 12 to 14 cm. each of the ribs ten, nine, and eight is excised near the vertebral column and the medial stumps are exarticulated. The periosteal sheaths, the intercostal muscles, vessels, and nerves are exposed and, apart from the nerves, removed. Dissection of the nerves is readily done as they course just below the periosteal sheath. In the following the procedure is the same as in the eight rib thoracoplasty, apart from the fact that, if the process has spread below the sixth rib, the second rib is excised like the first one up to the cartilage whereas the third rib will be resected subtotally.

As a rule, excision of large sections of the rib or their total removal can be done without technical difficulties. The fact that the inferior ribs have formerly been removed is an additional factor rendering the removal of the upper ribs easier.

Apicoplasty without apicolysis has been performed in 40 cases to date. Though the idea had been developed many years ago, it could not be executed on account of World War II, which interrupted the writer's usual work in thoracic surgery. Thus the work initiated could not be continued until the end of the war.

Of the 40 operated cases, three died. One patient died on the fourth postoperative day of myocardial failure; the second on the 3rd postoperative day of a pneumonitis involving the whole upper lobe; the third patient became the victim of a rapid progression on the twenty-seventh postoperative day. In two cases, the first stage was followed by a progression which prevented the performance of the second stage. In one case in which there was a cavity of 7 cm. in diameter

extending to the seventh rib, a residual cavity remained. In the other 34 cases, all symptoms disappeared within four months. These results are preliminary, as the longest follow-up since operation is only two years. Nevertheless the total mortality of 15 per cent seems favorable when compared with the immediate results with other methods.

The writer is aware of having committed the same error as other workers in thoracic surgery, *i.e.*, developing a "type operation", though the epoch of the "type operations" is over. Nevertheless, the results observed are at least as good as those observed after other operations. Moreover, as the mechanical, dynamic, and biologic factors influencing the pathologic process are not sufficiently known, a procedure practicable in nearly all cases seems to be advantageous.

It is realized that 40 cases do not suffice to form a final opinion for they might have constituted a lucky series which may be followed by less favorable cases. In the writer's opinion, however, optimism may be justified because of the fact that the cases operated on had not been selected.

#### SUMMARY

Thoracoplasty without apicolysis may result in restoration of the patient if the chest wall covering the pathologic process has been excessively mobilized by removing not only the first rib, but also the second rib, totally or subtotally, *i.e.*, to the cartilage. Exarticulation of the medial stumps is an additional factor which favors good collapse. If the operation is performed from below upward it is possible to do the second stage after the mediastinum has been fastened by cicatrization and, hence, complications resulting from a mobile mediastinum will not occur. Of 40 patients operated in this way, three died following operation, two suffered from rapid progression rendering the second stage impracticable, and in one case a residual cavity persisted. Thirty-four patients displayed clinical restitution having become free of symptoms within four months. Thus the operation was successful in 85 per cent of the cases.

#### SUMARIO

##### *Toracoplastia sin Apicolisis*

La toracoplastia sin apicolisis puede lograr el restablecimiento del enfermo si la pared torácica que recubre el proceso patológico ha sido extremadamente movilizada mediante la extirpación, no sólo de la primera costilla, sino también de la segunda, del todo o en parte, es decir, hasta el cartilago. La exarticulación de los muñones mediales constituye otro factor más en pro de un buen colapso. Si se ejecuta la intervención de abajo para arriba, es posible pasar a la segunda etapa después que la cicatrización ha fijado el mediastino, evitando así que sobrevengan las complicaciones debidas a un mediastino movable. De 40 enfermos operados en esta forma, 3 murieron después de la operación, 2 mostraron rápida agravación que impidió el segundo tiempo, y en un caso persistió una caverna residual. Treinta y cuatro pacientes manifestaron reposición clínica,



quedando asintomáticos en término de cuatro meses. La operación obtuvo, pues, éxito en 85 por ciento de los casos.

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## FOUR RIB APICOPLASTY WITH PLACING THE SCAPULA INTO THE THORAX

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It is common knowledge that 80 per cent of the tuberculous pulmonary lesions treated by operation are in the upper part of the lungs and one-fourth of latter are situated in the apex. Therefore, the idea of apicoplasty has been raised, virtually simultaneously, by various authors. Among the first of these were the French surgeons, Leriche and Bernou. Subsequently (1929) Walter Graf was active in this field. Bonniot, in 1927, was the first to remove the whole first rib whereby the technique of apicoplasty could be developed. It is rather difficult to define the conception of apicoplasty. Generally, by apicoplasty is meant a thoracoplasty involving four or at most five ribs while the lower half of the scapula is supported by the ribs left intact. The real apicoplasty most frequently performed is one involving four ribs because by this procedure a proper collapse of the apex can be brought about. Excision of the fifth or sixth rib is less frequently done because, with their removal, there is a danger that the scapula will fall obliquely forward, lie tightly on the intact ribs, and elicit pain by gliding on them to and fro. Furthermore, there remains, after an apicoplasty of such extension, a large dead space below the scapula. Consequently, it is wiser to perform an eight rib upper thoracoplasty instead of a five or six rib apicoplasty.

Surgical collapse therapy will not result in complete restoration of the patient unless the collapse of the part of the lung holding the cavity is complete. Restoration following an insufficient collapse may be due to a fortunate accident which should not be relied upon. The same principle also holds true for apicoplasty. The results of apicoplasty are, however, by no means completely satisfactory, as seen from the fact that from year to year modifications have been developed. Many workers have been engaged in developing a procedure likely to bring about a complete collapse of the pathologic process containing the cavity. Graf and Schmidt tried to substitute extrapleural pneumothorax or oleothorax for the apicoplasty. Although these procedures achieved collapse, they frequently failed to result in satisfactory recovery.

No doubt, the best method of treating an apical lesion is the eight rib upper thoracoplasty, following which the whole scapula sinks into the operated area. After an apicoplasty there remains, under the scapula, a dead space filled with blood and exudate. Later on, when these fluids have been absorbed, the collapsed apex would dilate whereby the result might be impaired. The process is the same as can occasionally be observed after apicolysis. The apicolysis associated with apicoplasty may involve another danger that there may be a downward migration of the cavity to a position where it would be distended again. In these cases, further ribs must be excised. The situation is even worse when the cavity is in the neighborhood of the "dead space" because in this

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case no correction would help. Overholt and Tubbs have suggested the excision of the lower part of the scapula in order to promote its fall into the thorax and thus prevent the dead space. Graf and Schmidt recommended the application of a supporting plomb in an effort to improve the procedures. These modifications have also failed.

The aforementioned drawbacks attending apicoplasty may be eliminated by Maurer's apicoplasty, in which the scapula is placed in the thorax.

The operation involves the upper four or five ribs. It is, in both cases, a two stage operation.

A nearly horizontal incision is recommended, starting at the level of the second rib near the vertebra and running slightly downward obliquely to the posterior margin of the axilla. A longitudinal incision, which is started paravertebrally with a slight lateral curve in its lower half, is similarly adequate. The incision mentioned first is more sparing of the muscles and also has cosmetic and functional advantages, but does involve considerable technical difficulties.

In the first stage of Maurer's two stage operation a paravertebral subperiosteal resection of ribs five and four over a section measuring about 14 cm. is made. Then the periosteal sheaths, together with the intercostal vessels, nerves, and muscles, are dissected off the pleura and removed in an extension corresponding with the resected ribs. The sixth and seventh intercostal nerves are prepared and a piece measuring 2 to 3 cm. of each of them is excised. These nerves are readily found near the spine if the periosteum of the ribs is incised and removed. The nerve is located at the lower border of the rib under the periosteum. This first stage is inefficient from the viewpoint of the collapse and its only action is the paralysis of the costal respiration at the middle portion of the chest, as a sequel of the nerve excision. The second stage should take place after three weeks. Starting from the scar of the first operation, the region of the three upper ribs to be excised is exposed. A 14 cm. segment is removed from the third rib and a 12 cm. segment from the second rib, while the first rib is excised to the cartilage. At this time the soft parts of the excised ribs are left in place. Afterwards an incision is made at the upper margin of the sixth rib. The layer containing the fascia endothoracica and the parietal pleura is bluntly prepared and the lung is extrapleurally separated with the finger from the sixth to the eighth ribs on both sides from the spine to the posterior axillary line. In this manner an extrapleural pouch of considerable size is created between the lung and the bony thorax in the region of the excised ribs. The posterior aspect of the lower half of the scapula is freed of the muscles which are inserted there and is energetically elevated and placed above the intact sixth rib into the extrapleural pouch. The scapula thus dislocated stands under the downward traction of the muscles of the shoulder girdle and hence will not return to its original place. The wound is closed primarily in the usual layers. The four rib variety of this operation is similar to the one described. In the first stage, paravertebral subperiosteal excision of the fourth and third ribs (14 cm. of each) is accomplished with the removal of the corresponding soft parts (intercostal muscles, vessels, and nerves) and a 2 to 3 cm. segment of the fifth and sixth intercostal nerves. In the second stage, 12 cm. of the second rib and the whole first rib are resected. The extrapleural pouch is formed from the fifth rib onward and the scapula is elevated and placed into the pouch as in the fifth rib variety. The scapula placed into the pouch will glide, with its posterior aspect, on the inner surface of the intact lower ribs. These movements will cause no pain, however, because the nerves of these ribs have been severed.

The Maurer procedure enhances the collapse of the apex by exerting a pressure

from behind forward. A further additional factor which facilitates collapse is the extrapleural separation of the lung. Maurer holds the view that this procedure accomplishes a thorough collapse, whereas the result of the operation is the same as that achieved by an eight rib thoracoplasty. He suggests a two stage operation for two reasons: first, there is a first stage representing very little strain only; second, it is a trial serving as a tolerance test and a test from which the reacting capacity of the process may be seen. The interval elapsing between the two stages need not be rigidly fixed because the result of the second stage will not be impaired by the rib regeneration following the first stage. Maurer suggests, however, an interval of at least six weeks.

The writer has made observations which indicate that Maurer's four rib apicoplasty should be done as a one stage operation.

In one case, a cavity was at the height of the removed third and fourth ribs and became distended after they were removed at the first stage. The lung underwent infiltration which extended throughout nearly the whole upper half of the lung. The nut sized cavity rapidly increased until, on the ninth postoperative day, profuse bleeding occurred and the patient died of suffocation. In another case, a pathologic process extending to the seventh rib unexpectedly healed after Maurer's four rib apicoplasty was performed in two stages. As to the first case, a one stage operation would very likely have resulted in a collapse which would have prevented the distension of the cavity and the rapid progression. Similar observations regarding two stage thoracoplasty have pointed to the critical interval between the two stages. Several authors (Sauerbruch, Brunner, Denk, Sebestény, and others) have reported that in about 10 per cent of all cases such a rapid progression ensues that fatal outcome is the rule. According to the writer's experience, this percentage is not exaggerated. Furthermore, attention is called to the fact that the double surgical exposure of a small area at a short interval will doubtless interfere with wound healing. Even in cases like the second one cited above, there is no advantage in dividing the operation into two stages because failure of the second operation involves the necessity of a third operation.

Because of the above considerations, the writer decided to perform Maurer's four-rib apicoplasty as a one stage operation. The paravertebral incision is started from the first rib and led downward to the fifth rib, then laterally along the fifth rib for a length of 8 cm. (figure 1). This incision yields a better exposure than the horizontal one. After severing the muscles, 16 cm. of the fourth rib, 15 cm. of the third rib, almost the whole second rib, and the whole first rib to the cartilage, are removed paravertebrally and subperiosteally. The medial stumps of the resected ribs are then exarticulated, in order to augment the collapse of the apex and to narrow the "dead space" near the spine (figures 2a and 2b). The first operations were performed without the exarticulation of the rib stumps and the resulting collapse was less complete (figures 3a and 3b). In the remainder of the operation, the fifth and sixth intercostal nerves are paralyzed, the lung is extrapleurally separated from the fifth rib downward and the scapula is placed into the thorax, as in Maurer's original operation.

As may be seen, there is a considerable difference between the writer's four



FIGS 1-3

rib apicoplasty and Maurer's corresponding operation. Apart from the fact that the operation is in one stage, larger pieces of the ribs are excised and the medial stumps are exarticulated so that the collapse of the apex and the lung is more complete and the "dead space" coming by the spinal column is narrower. These factors result in a greater effect of the operation. When it is considered that in the majority of cases the apical cavities are seated behind the spine, it is very important that collapse of this part of the apex be as great as possible. Despite the extrapleural separation of the lung and the displacement of the scapula, so that its pressure effect is fully operating, the writer's operation has not the same value as an eight rib thoracoplasty. Nevertheless, it may be very useful in cases of apical lesions which develop at the extreme apex.

The operation executed with the writer's technique exhibits a considerable resemblance to Graf's apicoplasty associated with pneumolysis. With the Graf technique, when the apex cannot be separated on account of firm adhesions, the four upper ribs are excised and exarticulated so that an extrapleural cavity is formed which extends downward as low as the extent of pathologic process. The wound is then closed and the subsequent treatment is like an extrapleural pneumothorax. The chief difference consists in the fact that Graf leaves the scapula outside the thorax, whereas the writer places it into the extrapleural pouch. Graf's operation is excellently tolerated, which was one of the principal reasons which induced the writer to perform Maurer's apicoplasty as a one stage operation.

The patients should be selected very carefully. Special attention should be directed to the condition of the mediastinum. Patients with a fixed mediastinum will tolerate the operation better. No serious functional disturbances have been observed following operation. Neither an exaggerated collapse nor paradoxical respiration occurred.

The real value of this operative procedure cannot be finally determined until it has been tried in a large series of patients.

#### SUMMARY

Maurer's four rib apicoplasty is well tolerated if performed as a one stage operation. Despite this, it is wise to select carefully the patients to be operated. Fixation of the mediastinum is associated with a better toleration of the procedure. Collapse of the apex can be considerably enhanced by exarticulation of the ribs. Functional disturbances have been rare, though the value of this technique cannot be judged before a long series of operations will have been performed.

FIG. 1. One stage four rib apicoplasty with the scapula placed into the thorax. Healed scar.

FIG. 2a. Cavernous apical process of the right side before operation.

FIG. 2b. The same case after a one stage four rib apicoplasty with insertion of the scapula into the thorax. Complete collapse due to the exarticulation of the rib stumps.

FIG. 3a. Cavernous apical process of the right side prior to operation.

FIG. 3b. The same case after a one stage four rib apicoplasty with insertion of the scapula into the thorax. The rib stumps have not been exarticulated. As compared with figure 2b, the degree of the collapse is less complete.

## SUMARIO

*Apicoplastia Cuadricostal con Colocación Intratorácica del Omoplato*

La apicoplastia cuadricostal de Maurer es bien tolerada si se ejecuta como operación en un tiempo, pero a pesar de esto conviene seleccionar cuidadosamente los casos. La mediastinopexia hace que el procedimiento sea mejor tolerado. El colapso del vértice puede acrecentarse considerablemente mediante la exarticulación de las costillas. Los trastornos funcionales han sido raros, aunque no puede juzgarse el valor de esta técnica antes de ejecutar una numerosa serie de intervenciones.

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# PROGNOSTIC SIGNIFICANCE OF OCCASIONALLY POSITIVE SPUTUM AFTER ADEQUATE TREATMENT OF TUBERCULOSIS<sup>1</sup>

Follow-up Study of Discharged Patients

ROBERT CHANG

## INTRODUCTION

The problems arising in the case of patients who occasionally discharge tubercle bacilli in the sputum, after apparently adequate therapy for tuberculosis, have been discussed in considerable detail by Stokes (1), Willis (2), McNett (3), and Soderstrom (4) from the clinical, pathological, nursing, and public health aspects. Speaking of the same question, Pinner (5) stated that: "One of the fundamental aspects of the problem is the question whether patients with arrested pulmonary tuberculosis and who never had any positive sputum or gastric cultures during their last six months of hospitalization have a better prognosis than patients who meet the same diagnostic requirements, but who had one or two positive cultures during their last half year of hospitalization. An answer to this question is not available at present. Only a significant prognostic difference would justify further treatment of the second group of patients." The purpose of this article is to attempt to find out such a prognostic difference from the available data at the Rutland State Sanatorium.

## PLAN OF INVESTIGATION

The data are based on the records of 621 patients suffering from the reinfection type of pulmonary tuberculosis, who were discharged as arrested or apparently arrested and who have been followed regularly for a period of two years or more after discharge between June 1935 and June 1945, inclusive. Patients who left the sanatorium in six months or less without evidence of activity during the whole period of hospitalization were excluded, as were those discharged with many cultures positive for tubercle bacilli during their last six months of hospitalization. Another 243 patients discharged between January 1932 and June 1935, inclusive, as apparently arrested, or arrested, are brought in for comparative study. Before 1935, cultures were performed too irregularly to be of much value, so the sputum specimens from this group of 243 patients were negative only on direct examination of smears and concentrates during the last six months of their sanatorium residence. Clinically and roentgenologically, the members of this group are comparable to those discharged from 1935 to 1945.

The exact meaning of "occasionally positive sputum" in this report is as follows. In the last six months of sanatorium residence, concentrated specimens from those patients whose sputum revealed no tubercle bacilli on stained smear were repeatedly cultured and occasionally inoculated into guinea pigs. At least six cultures of twenty-four to seventy-two hour specimens of sputum were made for each patient. When one or two of the cultures were positive for tubercle ba-

<sup>1</sup> From the Rutland State Sanatorium, Massachusetts Department of Health.



cilli, the patient was considered to have "occasionally positive sputum." In this study, patients are classified as arrested, or apparently arrested, regardless of one or two positive cultures, providing they meet with the requirements of the National Tuberculosis Association's diagnostic standard. In the records of the Rutland State Sanatorium, however, they are designated only as quiescent. Those in whom the source of the infectious sputum could be traced definitely to endobronchial lesions through direct bronchoscopic vision were not discharged unless the endobronchial lesions had apparently healed.

The 621 patients discharged as apparently arrested, or arrested, between 1935 and 1945 are divided into two groups. Group A consists of those with unequivocally negative sputum for the six months immediately preceding discharge. Group B consists of those with occasionally positive sputum. The 243 patients discharged between 1932 and 1935 with negative smears and concentrations make up Group C. Each group is subdivided according to the extent of the lesions on

TABLE 1

*The percentage of reactivation of the three groups of patients followed up for four years or more*

|                                | GROUP A*        | GROUP B†        | GROUP C‡        |
|--------------------------------|-----------------|-----------------|-----------------|
|                                | <i>per cent</i> | <i>per cent</i> | <i>per cent</i> |
| Minimal cases.....             | 11              | 21              | 21              |
| Moderately advanced cases..... | 20              | 32              | 38              |
| Far advanced cases.....        | 27              | 52              | 57              |

\* Group A represents patients with sputum negative on culture and guinea pig inoculation.

† Group B represents patients with occasionally positive sputum.

‡ Group C represents patients with sputum recorded as negative solely on the basis of examination of stained smears of individual or concentrated specimens.

admission. The number of patients followed and the number of patients reactivating in the first, second, third, and fourth, or more, years following discharge are tabulated.

#### RESULTS

As may be seen in table 1, the percentage of reactivation of Group B, patients with occasionally positive sputa, is comparable with that of Group C, those negative on smears and concentrations; while Group A patients, negative on cultures and guinea pig inoculation, have only half as many reactivations. The incidence of reactivations of patients followed for four years or more is 11 per cent in Group A, 21 per cent in Group B, and 21 per cent in Group C, for those admitted in the minimal stage. In the moderately advanced cases, the reactivation rate is 20 per cent for Group A, 32 per cent for Group B, and 38 per cent for Group C. In the far advanced cases, the rates are 27 per cent, 52 per cent, and 57 per cent for Groups A, B, and C, respectively. Stephens (6) reported an average recurrence rate of 28 per cent for those cured in the minimal stage and 43.3 per cent for those cured in the advanced stage (including both moderately

advanced and far advanced), when they were followed for five years after discharge. In the present study, the recurrence rates are distinctly lower than those reported by Stephens, especially in the Group A patients. It must be pointed out, however, that Stephens's report is based upon cases admitted between 1919 and 1938. The higher recurrence rates in the earlier cases may well be explained on the basis of less intensive treatment and lower requirements for discharge.

TABLE 2

*The frequency of reactivation of disease in tuberculosis patients in the first, second, third, fourth and subsequent years following discharge from the sanatorium*

| YEAR                      | GROUP A*           |                    |          | GROUP B†           |                    |          | GROUP C‡           |                    |          |
|---------------------------|--------------------|--------------------|----------|--------------------|--------------------|----------|--------------------|--------------------|----------|
|                           | Number of patients | Number reactivated | Per cent | Number of patients | Number reactivated | Per cent | Number of patients | Number reactivated | Per cent |
| Minimal cases             |                    |                    |          |                    |                    |          |                    |                    |          |
| First.....                | 97                 | 4                  | 4        | 20                 | 1                  | 5        | 49                 | 4                  | 8        |
| Second.....               | 93                 | 4                  | 4        | 19                 | 2                  | 10       | 45                 | 4                  | 9        |
| Third.....                | 63                 | 2                  | 3        | 13                 | 1                  | 8        | 40                 | 2                  | 5        |
| Fourth and more...        | 60                 | 0                  | 0        | 12                 | 0                  | 0        | 36                 | 0                  | 0        |
| Moderately advanced cases |                    |                    |          |                    |                    |          |                    |                    |          |
| First.....                | 193                | 11                 | 6        | 104                | 7                  | 7        | 124                | 13                 | 10       |
| Second.....               | 182                | 17                 | 9        | 97                 | 14                 | 14       | 111                | 17                 | 15       |
| Third.....                | 121                | 5                  | 4        | 83                 | 8                  | 10       | 90                 | 6                  | 7        |
| Fourth and more...        | 70                 | 2                  | 3        | 40                 | 3                  | 7        | 81                 | 9                  | 11       |
| Far advanced cases        |                    |                    |          |                    |                    |          |                    |                    |          |
| First.....                | 126                | 5                  | 4        | 81                 | 11                 | 14       | 70                 | 11                 | 16       |
| Second.....               | 121                | 13                 | 11       | 70                 | 18                 | 26       | 59                 | 14                 | 24       |
| Third.....                | 86                 | 8                  | 9        | 42                 | 6                  | 14       | 44                 | 6                  | 14       |
| Fourth and more...        | 50                 | 4                  | 8        | 28                 | 6                  | 21       | 31                 | 8                  | 26       |

\* Group A represents patients with sputum negative on culture and guinea pig inoculation.

† Group B represents patients with occasionally positive sputum.

‡ Group C represents patients with sputum recorded as negative solely on the basis of direct examination of stained smears of individual or concentrated specimens.

In table 2 may be seen the percentage of reactivation in the three groups of patients in the first, second, third, fourth, and subsequent years after discharge. The figures indicate that, in each year, Groups B and C patients reactivated more frequently than Group A patients. The strikingly higher percentage of reactivation in Group C patients in the fourth, and more, years after discharge, however, might be due to the longer period of follow-up. Stephens (6) reported recurrence rates of 2.4 per cent, 3.9 per cent, 3.8 per cent, and 3.3 per cent for her minimal cases followed in the fourth, fifth, sixth, and seventh years, respectively. In the present series, none of the 108 minimal cases, who had been negative for three consecutive years after discharge, have subsequently reactivated.

It is worth noting that the percentage of reactivation is highest in the second year for all three groups admitted in all stages. It must be pointed out that most of the patients of the present study resumed full working activity in six to twelve months after discharge. Whether this resumption of full working activity and the highest recurrence rate in the second year are merely incidental or related cannot be established at this time.

It might appear illogical that Group C patients should have as high a percentage of reactivation as Group B patients. If more intensive sputum studies had been made in this group of patients, who were discharged between January 1932 and June 1935, inclusive, with negative smears and concentrations, it would be anticipated that unequivocally negative sputum would be found in some cases and occasionally or frequently positive sputum in other cases during the last six months of sanatorium residence. Thus, from the viewpoint of sputum findings, the prognosis of some of the patients in this group should be as good as those in Group A; in some, the prognosis should be comparable to those in Group B; and in others, it should be worse than Group B. This might explain why Group C patients had as high a reactivation rate as Group B patients, instead of a lower percentage. The data are insufficient to establish whether the more extensive use of collapse therapy in the more recently treated group of patients could account for the comparatively high percentage of reactivation of Group C. As stated above, the strikingly high percentage of reactivation of Group C patients in the fourth and subsequent years might be a reflection of the longer period of follow-up.

A comparison of Group A and Group C indicates that otherwise comparable patients, discharged with negative sputum on culture and guinea pig inoculation, fare much better than those whose sputum is recorded as negative solely on the basis of direct examination of smears or concentrates. Ordway, Medlar, and Sasano (7) demonstrated that cultures and guinea pig inoculation of sputum and gastric washings, consistently negative on direct examination, yielded 35.4 per cent positive results. This means that 35.4 per cent of the patients discharged as apparently arrested, or arrested, according to the National Tuberculosis Association's diagnostic standard, are demonstrably infectious by culture or animal inoculation. In the present study it was found that such patients experience a reactivation of their disease twice as frequently as those whose sputum is negative on culture and guinea pig inoculation.

#### COMMENT

The future of each tuberculous patient depends on so many factors that prognostication is bound to be proved wrong in a certain percentage of cases. In this paper, many of the important factors known to have great importance regarding the future of discharged patients are neglected because it is not possible to consider all these factors in this kind of statistical study. It appears, however, that patients discharged with occasionally positive sputum do reactivate more frequently than those with unequivocally negative sputum, and that intensive sputum study in the six months immediately preceding discharge does help in the prognostication of the future of discharged tuberculous patients.

## SUMMARY

A follow-up study of 864 apparently arrested, and arrested, cases of tuberculosis is reported.

Recurrence rates of those with sputum negative for tubercle bacilli on cultures and guinea pig inoculation, those with occasionally positive sputum, and those with sputum negative on direct examination only, are compared. The latter two groups had a comparable recurrent rate which was twice that of the first group.

The highest recurrence rate was in the second year after discharge.

Patients discharged with occasionally positive sputum experience a reactivation of their tuberculosis more frequently than those with unequivocally negative sputum.

## SUMARIO

*Significado Pronóstico del Esputo Ocasionalmente Positivo después del Tratamiento Adecuado de la Tuberculosis*

Este estudio versa sobre la observación subsiguiente de 864 casos aparentemente estacionados y estacionados de tuberculosis.

Compáranse los índices de recurrencia entre los enfermos con esputo negativo para bacilos tuberculosos en cultivos y en el cobayo, los enfermos con esputo ocasionalmente positivo y los que mostraron esputo negativo sólo al examen directo. Los dos últimos grupos mostraron un índice comparable de recurrencias, que fué el doble del primer grupo.

El índice máximo de recurrencias correspondió al segundo año después del alta.

Los enfermos dados de alta con esputo ocasionalmente positivo manifiestan reactivación de su tuberculosis más frecuentemente que los que tienen un esputo claramente negativo.

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# THE SIGNIFICANCE OF POSITIVE CULTURES IN APPARENTLY ADEQUATELY TREATED PATIENTS WITH PULMONARY TUBERCULOSIS<sup>1</sup>

HANS ABELES<sup>2</sup>

## INTRODUCTION

The significance of the finding of a few tubercle bacilli in the sputum of the apparently adequately treated patient has been the subject of discussion in recent years. Pottenger and Pottenger (1) state "there is probably greater danger to the patient, himself, in the rare bacillus stage than to those who associate with him." The same authors "had a minimum of patients who have had a recurrence of clinical tuberculosis after being discharged as clinically well in spite of the presence of rare bacilli." Medlar and Reid (2), in their study of working ex-sanatorium patients found a "pauci-bacillary" sputum in a significant number of ex-patients. Pinner (3) and Rubin (4) stress the need for further investigation to shed some light on the question of a possible prognostic difference between the adequately treated patient from whom tubercle bacilli may be cultured occasionally, and the patient with completely negative bacteriologic findings.

In sanatorium work, the physician is frequently faced with the problem of the further management of the apparently adequately treated patient with arrested disease who occasionally discharges tubercle bacilli in the sputum. The question arises whether such a patient should be discharged, continue with sanatorium care, or undergo other forms of treatment.

It is virtually impossible to obtain patients comparable as to age, sex, race, family and social background, extent of disease, and form of treatment, who differ only as to the result of culture studies. Consequently, in an attempt to investigate this problem of the continued discharge of small numbers of tubercle bacilli, it was decided to study a large series of cases. It was thought that a large number would sufficiently compensate for individual differences to permit pertinent conclusions.

## OBSERVATIONS

*Clinical material:* The material consisted of 199 white patients discharged as apparently arrested, or arrested, from the Country Sanatorium of the Montefiore Hospital, Bedford Hills, New York, in the three year period from January 1939 to December 1941. All patients discharged as apparently arrested fulfilled the criteria of an arrested lesion with the exception of not having had the required amount of physical activity. All patients had a minimum of two cultures, including at least one gastric culture, within six months prior to discharge. During

<sup>1</sup> From the Country Sanatorium in Bedford Hills, New York, of the Montefiore Hospital<sup>1</sup> for Chronic Diseases, New York City.

<sup>2</sup> Bureau of Tuberculosis, New York City Department of Health, 125 Worth Street, New York 13, New York.

this period concentrated specimens of sputum were examined at least once a month but usually more frequently. The above postulates were fulfilled by 211 patients, but only 199 patients were included in the study as no satisfactory follow-up reports were obtained in 12 patients.

*Results of cultures:* One hundred and four patients were discharged with all cultures negative for tubercle bacilli during the specified period. The average number of cultures per patient in the six month period prior to discharge was 3.3. The remaining 95 patients had one or more cultures positive for tubercle bacilli in the six month period prior to discharge. Frequently only a single positive culture was obtained, followed by several negative cultures. Forty-six patients of this group, that is approximately one-half of all positive cases, were positive only on culture of the gastric washings.

*Extent of disease:* The extent of the disease at the time of discharge, and its relationship to the results of cultures during the six month period prior to discharge, are presented in table 1. The patients with moderately and far advanced tuberculosis were almost evenly distributed between the positive and

TABLE 1

*Extent of disease and result of cultures during the six month period prior to discharge*

| EXTENT OF DISEASE        | NUMBER OF PATIENTS DISCHARGED WITH |                   |
|--------------------------|------------------------------------|-------------------|
|                          | Positive cultures <sup>a</sup>     | Negative cultures |
| Minimal.....             | 6                                  | 18                |
| Moderately advanced..... | 36                                 | 34                |
| Far advanced.....        | 53                                 | 52                |
| Total.....               | 95                                 | 104               |

negative culture groups. Among the patients with minimal disease, three times as many were discharged with cultures negative for tubercle bacilli as with cultures which were positive.

*Period of observation:* The average period of observation following discharge for the patients discharged with negative cultures, who were not readmitted, was 43.6 months; for the ones discharged with positive cultures, who were not readmitted, the average period of observation was 45.3 months. The shortest period of observation was 29 months in either group; the longest was 62 months in the former group, and 64 months in the latter group.

*Follow-up observation:* Thirty-six of the 199 patients were readmitted to a sanatorium or treated at home for reactivation of their disease. For practical purposes they will be referred to as readmitted patients. Twenty-five of the readmitted patients had positive cultures and 11 had negative cultures during the six month period prior to discharge. The cumulative rate of readmitted patients discharged with positive cultures was 28.5 per cent, and of readmitted patients discharged with negative cultures, 10.5 per cent at the end of four years of observation (table 2). The difference in these cumulative percentages of

TABLE 2

*Cumulative percentages of readmitted patients during four years after discharge according to culture results during the six month period prior to discharge\**

| MONTHS AFTER DISCHARGE  | CUMULATIVE PERCENTAGES OF READMITTED PATIENTS DISCHARGED WITH |                   |
|-------------------------|---|-------------------|
|                         | Positive cultures   | Negative cultures |
| First six months.....   | 2.1   | 1.0               |
| Second six months.....  | 12.1  | 2.0               |
| Third six months.....   | 15.3  | 4.9               |
| Fourth six months.....  | 20.7  | 7.8               |
| Fifth six months.....   | 22.9  | 7.8               |
| Sixth six months.....   | 25.4  | 9.0               |
| Seventh six months..... | 28.5  | 10.5              |
| Eighth six months.....  | 28.5  | 10.5              |

\* Readmitted patients cease to be part of the patients at risk.

TABLE 3a

*Number of readmitted patients discharged with positive cultures by stage of disease on discharge and treatment*

| TREATMENT          | STAGE           |                 |                     |                 |                 |                 | TOTAL           |                 |
|--------------------|-----------------|-----------------|---------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                    | Minimal         |                 | Moderately advanced |                 | Far advanced    |                 |                 |                 |
|                    | Dis-<br>charged | Read-<br>mitted | Dis-<br>charged     | Read-<br>mitted | Dis-<br>charged | Read-<br>mitted | Dis-<br>charged | Read-<br>mitted |
| Bed-rest.....      | 5               | 1               | 19                  | 6               | 9               | 4               | 33              | 11              |
| Pneumothorax.....  | 1               | 0               | 15                  | 4               | 30              | 8               | 46              | 12              |
| Thoracoplasty..... | 0               | 0               | 2                   | 0               | 14              | 2               | 16              | 2               |
| Total.....         | 6               | 1               | 36                  | 10              | 53              | 14              | 95              | 25              |

TABLE 3b

*Number of readmitted patients discharged with negative cultures by stage of disease on discharge and treatment*

| TREATMENT          | STAGE           |                 |                     |                 |                 |                 | TOTAL           |                 |
|--------------------|-----------------|-----------------|---------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                    | Minimal         |                 | Moderately advanced |                 | Far advanced    |                 |                 |                 |
|                    | Dis-<br>charged | Read-<br>mitted | Dis-<br>charged     | Read-<br>mitted | Dis-<br>charged | Read-<br>mitted | Dis-<br>charged | Read-<br>mitted |
| Bed-rest.....      | 17              | 5               | 7                   | 0               | 5               | 0               | 29              | 5               |
| Pneumothorax.....  | 1               | 0               | 22                  | 3               | 39              | 3               | 62              | 6               |
| Thoracoplasty..... | 0               | 0               | 5                   | 0               | 8               | 0               | 13              | 0               |
| Total.....         | 18              | 5               | 34                  | 3               | 52              | 3               | 104             | 11              |

readmission is statistically significant. It is not accounted for by the stage of the disease, nor by the type of treatment. Although there is a trend toward a higher

rate of readmissions in the patients treated by bed-rest, as compared to the ones treated by collapse therapy (pneumothorax and thoracoplasty), the difference is not statistically significant (tables 3a, 3b).

The largest number of readmissions occurred within the two year period following discharge. The average period between discharge and readmission was 22.9 months for the patients discharged with negative cultures, and 17.6 months for the ones discharged with positive cultures. In the first group, the shortest period between discharge and readmission was 3 months, the longest 50 months; in the second group, it was 6 months and 41 months, respectively.

TABLE 4

*Number of readmitted patients by discharge according to positive sputum or gastric culture, respectively*

|   | POSITIVE CULTURE ON DISCHARGE |                 |                            | TOTAL |
|---|-------------------------------|-----------------|----------------------------|-------|
|   | Sputum culture                | Gastric culture | Sputum and gastric culture |       |
| Number of patients discharged . . . . . | 37                            | 46              | 12                         | 95    |
| Number of patients readmitted . . . . . | 7                             | 14              | 4                          | 25    |

TABLE 5

*Bacteriologic findings of the 36 readmitted patients during the six month period prior to discharge and during second hospitalization*

| CULTURE RESULT DURING 6 MONTH PERIOD PRIOR TO DISCHARGE | NUMBER OF PATIENTS | BACTERIOLOGIC <sup>1</sup> FINDINGS DURING SECOND HOSPITALIZATION | NUMBER OF PATIENTS |
|---|--------------------|---|--------------------|
| Negative . . . . .                                      | 11*                | positive<br>negative  | 9**<br>2           |
| Positive . . . . .                                      | 25                 | positive<br>negative  | 24***<br>1         |

<sup>1</sup> This includes results obtained by direct examination or culture.

\* Four patients were negative during the entire period of hospitalization.

\*\* Two patients were positive only on culture.

\*\*\* Four patients were positive only on culture.

Three patients died. The time interval between discharge and readmission for the fatal cases was 15 months and 20 months for two patients discharged with positive cultures, and 3 months for the one discharged with negative cultures.

Of the 46 patients who were positive for tubercle bacilli only on gastric culture during the six month period prior to discharge, 14 were readmitted (table 4). The bacteriologic findings during the entire period of second hospitalization are given in table 5.

*Cause of readmission:* The immediate reason for readmission was progression in serial roentgenograms in all 11 patients discharged with negative cultures. Two of these patients had, in addition, a positive sputum on direct smear when re-



admitted. Of the patients discharged with cultures positive for tubercle bacilli, 21 had roentgenologic changes and 4 had positive sputum on examination of direct smear or of smears of concentrated specimens, at the time readmission was advised.

#### COMMENT

While patients whose sputum is positive only on culture discharge fewer tubercle bacilli than those whose sputum contains organisms demonstrable on direct smear, the dividing line is arbitrary. The results of this study indicate that the apparently adequately treated patient, whose sputum is negative on culture during the six month period prior to discharge, has a greater probability to stay well than the one who has occasional positive cultures during the same period. The validity of the classification, pulmonary tuberculosis, arrested, in the presence of cultures positive for tubercle bacilli, is therefore open to question.

Although each case has to be evaluated individually, it seems advisable to make every effort to achieve complete bacteriologic conversion in patients with recent active disease. While in some cases prolongation of the treatment may be successful, in others, a change in the type of treatment may be advisable. In any event, there will still remain a group of patients for whom no further treatment is possible for one reason or another. For this group the physician will have to be content with a satisfactory clinical result without sputum conversion. These patients should have very close medical supervision for a larger number of reactivations may be anticipated in this group than in patients who become noninfectious.

It should be emphasized that this study is concerned only with patients with recent active disease who were apparently adequately treated. The problem of the ex-patient who has been well for years but who has a "pauci-bacillary" sputum on certain occasions is possibly a different matter. On the basis of clinical impressions, it would seem that the prognosis of the latter type of patient is good.

A possibly significant finding of this study was that 14 of 46 patients discharged after apparently adequate treatment and who were positive for tubercle bacilli only on gastric culture were readmitted for reactivation of their disease. Some of these patients raised no sputum, others might have yielded positive sputum cultures if their sputum had been studied more intensively. Further studies as to the prognostic significance of positive gastric cultures as compared to sputum studies in the apparently adequately treated patient are indicated.

#### SUMMARY

1. A study was undertaken to evaluate the significance of cultures positive for tubercle bacilli in apparently adequately treated patients discharged from a sanatorium.

2. One hundred and ninety-nine patients, discharged as apparently arrested, or arrested, were observed for an average period of forty-four months. One hundred and four patients had only negative cultures and 95 patients had occasional positive cultures during the six month period prior to discharge.

3. The cumulative rate of readmissions at the end of four years following discharge was 28.5 per cent for the patients discharged with positive cultures, and 10.5 per cent for those discharged with negative cultures.

#### SUMARIO

#### *La Significación de los Cultivos Positivos en Tuberculosos Pulmonares Aparentemente Tratados Adecuadamente*

1. Este estudio fué emprendido para justipreciar la importancia que revisten los cultivos positivos para bacilos tuberculosos en enfermos aparentemente tratados adecuadamente y dados de alta de un sanatorio.

2. A 199 enfermos, dados de alta como aparentemente estacionados o estacionados, se les observó, por término medio, durante 44 meses. Ciento cuatro enfermos sólo mostraron cultivos negativos en tanto que 95 mostraron de cuando en cuando cultivos positivos durante los seis meses anteriores al alta.

3. El coeficiente acumulativo de reingresos al cabo de los cuatro años consecutivos al alta fué de 28.5 por ciento para los dados de alta con cultivos positivos, y de 10.5 por ciento para los dados de alta con cultivos negativos.

#### *Acknowledgments*

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# PUBLIC HEALTH SIGNIFICANCE OF RARE TUBERCLE BACILLI IN SPUTUM<sup>1</sup>

F. M. POTTENGER<sup>2</sup>

## THE RARE BACILLUS STAGE

For the past thirty years at the Pottenger Sanatorium the dilution-flotation-picro-acid technique (1) has been employed for the examination of sputum.

By examining three day specimens every six weeks, it has not been possible to demonstrate an absence of bacilli for three consecutive examinations in more than four or five per cent of the patients at the time of discharge from the sanatorium. In contrast, many institutions report sputum conversion in fifty per cent or more. Although most of our patients have far advanced tuberculosis, we also have had many who had earlier lesions. Many of these on entering had been classed as having negative sputum, some after many examinations. After admission to the sanatorium, however, examination of the sputum revealed the presence of tubercle bacilli in nearly all of this group.

When these patients with "rare bacilli" are discharged they are physically well and able to walk from one to four or five miles a day. They rarely cough. It is often only with the greatest persistence that specimens of sputum are obtained.

In order to determine the epidemiological significance of "rare bacilli", a comparison might be made between the "rare bacillus" stage and the situation when these patients are expectorating bacilli freely. The Phipps Institute (2) reports on 158 twenty-four-hour specimens from 37 patients. The average twenty-four-hour output of bacilli for white patients was 129,593,000; for Negro patients 894,000,000. The highest count was 20,499,918,000. J. E. Pottenger (3) studied a patient's output of bacilli for several days. The counts were 128, 130, 133, 83, 98, and 131 million. Another patient's count was 30 billion.

In table 1 may be seen the results of bacillary counts of the sputum made at six week intervals in patients now in the sanatorium. The first six have attained the "rare bacillus" stage; the last two are wholly in the acute stage. The figures indicate the number of bacilli expectorated in twenty-four hours. The first six cases were steadily improving, but it will be noted that the decline in numbers of bacilli was not steady. Patients E. T. G., S. D., and J. S. all had cavities which were healing spontaneously. Patients S. A., P. O., and A. H. were minimal cases in whom tubercle bacilli had not previously been found.

J. E. Pottenger (4) made careful comparison of the dilution-flotation-picro-acid and the Ziehl-Neelsen techniques for the examination for tubercle bacilli and found the former 277 times more sensitive in purulent sputum, and 172 times more sensitive in "mucop-epithelial" sputum. This sensitive technique may reveal tubercle bacilli when the patient expectorates only a few hundred or a thousand bacilli a day.

<sup>1</sup> Presented before the Epidemiology Section of the American Public Health Association, Atlantic City, October 6, 1947.

<sup>2</sup> Monrovia, California.

How dangerous is sputum which contains a few hundred or a few thousand bacilli in a twenty-four-hour quantity? Frankly, no one knows because conditions differ so greatly, but surely it can not be very dangerous. If the patient knows he has, or has had, tuberculosis, as a rule the sputum is destroyed. In fact, when the sputum decreases to a very small amount it is often swallowed unknown to the patient. If a few hundred or a few thousand bacilli should be expectorated into a room, however, they would be diluted by the air which, if the room is well ventilated, is constantly changing, so the danger would be minimal. Under ordinary conditions of light and ventilation in the average house, most bacilli would be killed in a few hours. It must be admitted, however, that there might be danger in overcrowded, poorly ventilated houses, particularly those occupied by the undernourished.

TABLE 1

*Daily output of tubercle bacilli in sputum of patients with pulmonary tuberculosis*

|   | PATIENTS |  |
|---|----------|--|
| 1 | E. T. G. | 3,900,000,000—1,500,000—3,000,000—50,000,000—21,000—500,000—9,300—9,340,000—1,200,000—3,266—0—0—875—892—0—0—0. |
| 2 | S. A.    | 825—0—0—0—536—0—0—0—14,700—0.  |
| 3 | S. D.    | 1,700,000—10,600,000—4,200,000—9,250—16,800—12,000,000—40,385—64,100—38,500—3,260—112,700.                     |
| 4 | P. O.    | 11 days, 0—1,458—13,416—0—13,880—0.  |
| 5 | J. S.    | 2,800,000—5,100,000—2,000,000—46,000,000—2,340—5,540—1,106—0—0.  |
| 6 | A. H.    | 0—3,266—0—0—0—0—4,375—0—0—0—0.   |
| 7 | L. G.    | 80,000,000—5,000,000—47,000—171,000,000—137,000,000—95,000,000.  |
| 8 | G. H.    | 190,000,000—267,000,000—64,000,000—385,000,000—240,000,000—7,800,000,000.                                      |

According to the studies at the Pottenger Sanatorium, it is doubtful whether patients with chronic destructive lesions ever become wholly and continuously free from the discharge of tubercle bacilli under all of the vicissitudes of life; yet they may be able to carry on their work unhampered. Many ex-patients have been followed from five to forty years and it has been found that now and then, particularly following acute respiratory infections, they will cast off a few tubercle bacilli as a result of the stimulation of their old foci. These patients usually become noninfectious soon after recovery from the acute respiratory infection without reactivation of their tuberculous disease and without causing disease in others (5). It is not the controlled patient, but the one who is not cognizant of his disease or the careless one, who is most dangerous to himself and to others.

Our experience is similar to that of Papworth Village (6) in England, which indicates that it takes more than the expectorating of bacilli to cause infection. The report of twenty-five years' experience shows that, of 108 children born in

Papworth Village, not one has developed active tuberculosis, nor has radiologic examination revealed an incidence of pulmonary abnormalities any higher than that found in the general population. Nevertheless, 90 of Papworth's 120 patients suffered from "open" tuberculosis. Of 260 children born before admission to the Village (in the usual city workman's environment), 5.1 per cent had some type of active tuberculosis. These had lived outside the Village in the environment of "open" tuberculosis. Of these children, 8 were over 10 years of age on entering the Village. It is significant that no new cases of active disease developed among them after entering the Village.

This shows the protective value of the control of patients living in a controlled environment, for it must be remembered that all of these children had hereditary susceptibility and many were living in an environment of "open" tuberculosis. Are we to conclude that infection and reinfection can be partly, possibly largely, prevented by living hygienically even in an infected environment? If so, where is the danger line? This is of greater importance than the simple fact of the presence of tubercle bacilli. May this not be interpreted that "rare bacilli" in controlled patients living in a controlled environment are of little danger?

#### HOW MANY BACILLI WILL INFECT?

The number of bacilli that will cause infection varies according to their virulence and the susceptibility and environment of the host. It is likely that many attempts at invasion are made before infection occurs, especially in hosts of low susceptibility. The important fact is that under conditions which exist many infections do occur. But more important is the fact that there are fewer instances of disease than of infection. This might indicate that the patient protects himself through primary infection.

The host is protected by monocytes and polymorphonuclear leucocytes which engulf and destroy bacilli and conceivably may possess some degree of humoral immunity. The cellular protection is greatly increased in the immune host, making reinfection more difficult, as shown by Lurie (7). Lurie reports that tuberculosis in rabbits removed from an infected environment as soon as sensitization has been acquired pursues the same course as in litter mates which continue in the infected environment.

Whether the bacilli enter the body as dust or droplets is of minor importance. The fact is that bacilli can produce primary infection whenever a sufficient number are able to enter the body, provided they find conditions favorable to growth. Bovine bacilli cause infection by entering otherwise than through the air channels, which is significant. If bovine, why not human? Who knows the portal of entry in chance infection?

#### EFFECT OF ENVIRONMENT ON BACILLI AND HOST

The infectiousness of bacilli depends largely on the environment in which they are discharged. They do not multiply outside the body, and many are non-virulent and many are nonviable when discharged. Even virulent bacilli are quickly destroyed by direct sunshine and within a few hours by indirect sun-

light. They live much longer in dark places when protected from drying. Their infectivity is favored by the dead air of nonventilated rooms and is very much reduced by moving currents of air.

In spite of the danger of infection in massively contaminated environments, those living therein do not all die of tuberculosis. Most of them are infected but do not develop clinical disease. This is a most significant fact in our program of prevention. It should be stressed, for it is the basis of protective vaccination. Throughout the ages not only were precautions rarely taken, but conditions of the premises were most favorable for the bacillus. Nevertheless, only about one new case developed regularly to each death and, wherever the social and economic status of the people improved, the number of deaths decreased. *Immunity and low susceptibility were a little more effective than the bacilli of reinfection.*

Children are most susceptible and are prone to receive a primary tuberculous infection whenever exposure is prolonged. This carries with it an immunity, however, which provides increased protection. But the danger of metastases from primary infection lies in the fact that tubercle bacilli may remain viable and virulent for years in many of these foci and in metastases which form from them. At any time that the architecture of the encapsulating wall is disturbed either mechanically or chemically, endogenous reinfection may be produced. This shows the necessity of knowing every infected child and making it the ward, so to speak, of the Health Department. Such children should be re-examined periodically, according to a plan based upon our knowledge of the significance of primary infection.

The greatest danger is always found among the poor, where from five to seven times as many deaths from tuberculosis occur as among families who live on a higher economic and social plane. This means that the poor patient with tuberculosis is a maximum danger to himself and his associates. Moreover his chances of healing are less, for both his environment and possibly his tissues are more favorable to the life of the bacillus. Public health measures, short of an effective vaccination, will not stamp out tuberculosis among the poor until it solves the problems of nutrition and housing; for poor nutrition and unhygienic homes increase susceptibility. Why let infected children go on to reinfection tuberculosis when a few simple rules of hygiene and a quart of milk a day would probably save many of them and save the taxpayers the expense of caring for well-developed cases of tuberculosis subsequently?

#### SUSCEPTIBILITY

It must not be forgotten that susceptibility is as important as the tubercle bacillus. Regardless of all public health factors with which people are protected, infection still occurs. Furthermore, it occurs whether or not it can be shown that the host associated intimately with "open" tuberculosis. Two-thirds of the clinical cases at the Pottenger Sanatorium give no history of associating with tuberculous patients. The only reasonable interpretation for this fact is that infection depends much upon the patient's susceptibility. Chance infection is undoubtedly caused by a few tubercle bacilli entering the tissues of a highly

susceptible individual. To be sure, infection of one living with a patient who expectorates hundreds of millions of bacilli a day may occur no matter what the susceptibility of the individual. Probably no one is so resistant that he is able under all circumstances to ward off infection. But, on the other hand, the possibility must not be overlooked that primary infection caused by many bacilli may establish a higher degree of immunity than the few bacilli of chance infection. This is indicated by the Lübeck disaster mentioned below. *May primary infection not have been the protective factor which has preserved the human race throughout the ages?* Does not this suggest vaccination as a way of protecting those nonreactors who live with patients who expectorate rare bacilli, as well as those who expectorate many?

How can all these facts be interpreted and what is their public health significance? Puffer's studies (8) have shown that *hereditary* susceptibility, which probably is similar or the same as general susceptibility, makes the host especially prone to infection. In the families which she studied, the same percentage of children of tuberculous parents who had, and who had not, associated with "open" tuberculosis developed clinical disease by the time they attained the age of fifty. The difference between the two groups was that those who were exposed by intimate association became ill in their earlier years, while those casually exposed developed the disease later. This might suggest that, regardless of the fact that those infected by many bacilli may develop a higher grade of immunity than those infected by a few, yet massive infection doubtless causes larger foci. These larger lesions contain larger numbers of bacilli and become less completely encapsulated and, hence, are more susceptible to injury by the vicissitudes of environment, growth, habits and other infections. Consequently, the patient with such a lesion is more apt to break down with clinical tuberculosis, particularly in the earlier years.

During the period between 15 and 25 years of age, the number of cases of clinical tuberculosis takes a rapid rise. This is the period when acute exudative tuberculosis predominates, a type caused by relatively large numbers of bacilli in patients whose cells are highly sensitized. The massive numbers of bacilli which cause this type of disease could well be endogenous in origin, but could hardly come from without. In the experience of the writer, these acute exudative cases are rarely associated with "open" tuberculosis at the time of falling ill. So we must assume, or at least bear in mind, that the source may be the unhealed primary complex, or some metastasis therefrom, whose enveloping walls are subject to injury by both mechanical and chemical factors.

In this connection, it must be remembered that the lung doubles in size from the beginning to the end of puberty. This may be a mechanical factor in reactivating old foci. *Clearly a partly or wholly calcified focus cannot expand and increase in size as the pulmonary and bronchial tissues do. The result might be a weakening or a break in continuity of the encapsulating walls with the escape of bacilli.* Moreover, in this period the tissues must also bear many insults, such as those from malnutrition, unwholesome habits of life, and so forth, just such as will further weaken an already weakened enveloping wall. This is a period of high incidence of clinical tuberculosis, much of it being of the acute exudative

type. The chronic proliferative type, on the other hand, advances slowly, probably because fewer bacilli cause the metastases and gradually immunize and desensitize the patient so that fibrosis predominates over inflammatory processes. This is the predominant form of the disease in later life.

Thus susceptibility seems to be a factor in infection, reinfection, the type of disease, and the outcome of the disease.

#### VACCINATION AGAINST TUBERCULOSIS

In the future, susceptibility, the protective value of the primary complex, and vaccination, must be given more consideration in providing a program for protecting the people from tuberculosis. Mass roentgenographic studies of the population must be continued, but as susceptibility, both that of a general and hereditary nature, is so important, the finding of those infected will still leave the problem unsolved. Susceptibility must be reduced and preventive vaccination must be generally used among those exposed.

When reinfecting bacilli attempt invasion, the host is able to destroy many more in the case of first invasion. Moreover, if reinfection occurs, it has a tendency to localize and heal, as pointed out by Koch in 1890-1891. Manwaring (9) has shown that, within an hour after tubercle bacilli are injected into the peritoneal cavity of an immune guinea pig, nine-tenths of them have been destroyed. Quite the opposite from the experiment of J. E. Pottenger (10), in which he infected two-thirds of a group of nonimmune experimental pigs by injecting three tubercle bacilli more or less into the peritoneal cavity.

It would seem that the danger to individuals who are protected by a previous infection, either primary or of the reinfection type, in associating with tuberculous patients is negligible, particularly if they are following out the accepted regimen used in treatment. The writer has never recognized an infection transmitted from a patient with active disease to one who was approaching arrestment, although free association of patients in the sanatorium has been observed for more than forty years.

It is possible that the great numbers of bacilli in massively infected environments, by destroying the most susceptible, have kept the tuberculosis mortality high throughout the ages, and by the same process produced a more resistant stock. On the other hand, wherever we have had an improved environment, susceptibility decreased and morbidity and mortality declined.

It must have been decreased susceptibility that reduced the death rate from tuberculosis in England and Wales from 330 per 100,000 population in 1860 to 175 in 1900, for few preventive measures were applied to make the patient's environment safe. In the forty years since 1900, preventive measures have been instituted but, because of war, the decline has been only a little greater than during the years 1860 to 1900, reaching a death rate of 70 per 100,000 in 1936. In Massachusetts the death rate declined from 444 in 1860 to 254 in 1900, and then, with the institution of preventive measures, the decline, unaffected by war, has been much greater. A death rate of 36 was reached in 1939.

*We should develop a more rational attitude toward primary infection. We should show more appreciation of its protective nature. We should likewise appreciate*



*that it carries with it, unless it heals or remains quiescent, the danger of being the source of endogenous metastases, responsible for much, possibly most, clinical disease.*

Were it not for its being the source of acute illness, such as meningitis in small children, and endogenous reinfection later, we might accept it as almost wholly protective. But since it is also a danger, we must, if possible, avoid it.

The use of BCG will stimulate immunity, probably not as efficiently as virulent human bacilli, but sufficiently to protect most children from infection. Moreover, it carries no danger of causing endogenous reinfection. Doubtless vaccination should be repeated the same as in case of smallpox. Vaccination should not take the place of other measures but should supplement them.

For those who have inordinate fear of infection or of protective vaccination, I would suggest the study of the Lübeck disaster, where virulent human bacilli were accidentally substituted for BCG. Two hundred and fifty-two children, before they were ten days old, were each given a total of 1,200,000,000 living human bacilli orally in three doses of 400,000,000. According to general opinion, all should have died; but instead 175 were living and well four years after. All were infected, but 70 per cent had developed sufficient resistance to prevent the spread of the disease.

#### FUTURE PROGRAM

Aside from all the things we are now doing to prevent infection, let us broaden our views. Let us reduce susceptibility both through vaccination and improvement in environment. An effectual program would consist of: (1) mass roentgenographic studies until every individual has received the benefits which it offers; (2) clearing the slums in which most of our tuberculosis is found; (3) teaching people how to live and what to eat, and furnishing food, at least to children, when the breadwinner is ill, so that resistance is kept high; and (4) vaccinating children, thus stimulating their immunity without producing a focus of living human bacilli within the tissues from which the disease may spread and produce endogenous reinfection. *We can not take the patient with "rare bacilli" out of society, but we can make him safe by instruction, and those who associate with him safe by vaccination, hygienic living, and adequate diet.*

#### SUMMARY

1. The "rare bacillus" stage of tuberculosis, with the discharge of a few hundred or a few thousand bacilli per day, is compared with the acute stage in which millions and even billions of bacilli are discharged per day.

2. There is a question whether patients with chronic destructive lesions would ever become continuously and permanently free from the discharge of bacilli, if techniques for examination were sufficiently sensitive, even though the patients might be clinically well and able to carry on their regular work.

3. As about two-thirds of clinical patients give no history of association with "open" tuberculosis, the individual to be infected must be considered as well as the one who scatters infection.

4. The importance of susceptibility is compared with that of environment in causing illness. Mortality from tuberculosis dropped about 50 per cent between

1860 and 1900 before active measures for protecting against infection were instituted in both England and Wales, and in Massachusetts in this country.

5. Vaccination should be used generally, but especially to protect those highly susceptible, those exposed to "rare bacilli" as well as to massive infection. BCG carries with it no danger of providing an endogenous source of reinfection.

#### SUMARIO

##### *Significación Sanitaria de la Rareza de Bacilos Tuberculosos en el Espujo*

1. Compárase la etapa de "bacilos raros" en la tuberculosis, en la que sólo se expulsan algunos centenares o miles de bacilos diarios, con la etapa aguda, en la que se expulsan millones, y hasta miles de millones, al día.

2. Cabe dudar si los enfermos con lesiones destructoras crónicas jamás cesarán continua y permanentemente de expulsar bacilos, si se emplean técnicas suficientemente de licadas para descubrirlos, aun cuando los sujetos estén esten clínicamente bien y puedan desempeñar sus tareas habituales.

3. Dado que dos terceras partes de los enfermos clínicos no comunican antecedentes de asociación con tuberculosis "abierta," hay que considerar al individuo infectable por igual que al infeccioso.

4. Compárase la importancia patógena de la susceptibilidad con la del ambiente. La mortalidad tuberculosa descendió aproximadamente 50 por ciento entre 1860 y 1900, antes de iniciarse medidas activas de protección contra la infección, tanto en Inglaterra como en Gales y en Massachusetts en Estados Unidos.

5. Debe emplearse generalmente la vacunación, pero más en particular para proteger a los muy susceptibles, a los expuestos a "bacilos raros" así como a infección masiva. BCG no entraña riesgo de aportar un foco endógeno de reinfección.

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# CLOSURE AND HEALING OF TUBERCULOUS CAVITIES<sup>1</sup>

JOHN LOESCH

## INTRODUCTION

In a previous communication (1), the diversified final patterns of the pathology of complete cavity closure were reported as they occurred in six instances in five cases. Briefly, the individual cavity became converted to a caseous inspissated focus enveloped by a fibrotic capsule, and the cavitary-bronchial communication with one or more draining bronchi was obliterated. In five cavities the process took place under pneumothorax treatment and in one on bed-rest. The length of time from institution of the treatment to the final termination ranged in three cases from eight months to two years, with the individual cavity diameters ranging from 1.5 to 3 cm. In two, the period of observation was about five to six years, with the cavities measuring 4.5 x 4.5 cm. and 7 x 5 cm. in diameter, respectively.

## MATERIAL AND METHODS

In the following study, five additional instances of cavity disappearance in four cases are reported. In the first two instances (Case 1, left upper lobe, and Case 2), the cavities became closed under therapeutic pneumothorax. In the remaining three, however, the cavities had actually healed by scar tissue. This complete anatomical healing occurred in the third instance (Case 1, right upper lobe) under pneumothorax, in the fourth (Case 3), on bed-rest, and in the fifth (Case 4), on bed-rest after the cavity had disappeared under brief pneumothorax which had been followed by effusion during optional re-expansion.

The methods of the morphological and histological study and the staining technique employed were in all cases essentially the same as used and described in the previous study (1). From 200 to 400 serial sections were examined of each area containing the former cavity.

## CASE REPORTS

*Case 1:* The patient (M. S.) was a white male of 42 years of age. The onset of the disease was in the early autumn of 1932 with night sweats and productive cough. Roentgenographic examination on February 2, 1933, showed an exudative infiltration in the right upper lobe enclosing a cavity measuring 3 x 3.5 cm., slightly above and about 1.0 cm. behind the second anterior rib (plate II, figure 1). Therapeutic pneumothorax was induced at the beginning of April 1933. The cavity shrank gradually (plate II, figure 2) and was no longer visible by June 1934. The involved area appeared as a sharply delineated opacity on a chest film taken on February 16, 1935 (plate II, figure 3) and thereafter. In February 1935, fluid appeared, which later changed into an empyema. The latter was drained by anterior thoracotomy in October 1937. In July 1935, a cavity began to form in an infiltrate in the third interspace on the left and measured 4 x 4 cm. on a film of February 2, 1937 (plate I, figure 1). Therapeutic pneumothorax was induced shortly

<sup>1</sup> From the Laboratory of The Homer Folks Tuberculosis Hospital, Oneonta, New York.

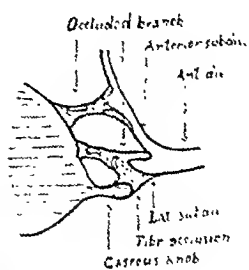
thereafter. This cavity was much smaller by May 25, 1937, and subsequently disappeared. On a film taken on August 16, 1937, the area of previous cavity appeared as a round opacity about 1.5 cm. in diameter. The opacity persisted during the following years but became much more sharply delineated and "harder" (plate I, figure 2). In December 1943, a bronchopleural fistula was demonstrated on the right. Between February 16, and April 20, 1944, a three-stage thoracoplasty was performed. The patient expired suddenly May 17, 1944, from a cerebral hemorrhage into the fourth ventricle.

*Postmortem findings:* The left lung was very emphysematous, especially in the lower lobe. On cutting this lung in 1.0 cm. thick layers in the coronal plane in the axis of the left stem bronchus, a caseous focus was found in the mid-portion about 0.5 cm. beneath the pleura and about 7.5 cm. from the summit of the upper lobe. The focus measured about 2.0 cm. in width and 1.5 cm. in height. It was caseous in the center and was enveloped by a fibrotic capsule (plate I, figure 3). On tracing the bronchi, it was found that the lateral subdivision of the anterior division terminated about 0.5 cm. from this focus and a branch of the anterior subdivision was occluded beyond its branching-off point.

On microscopic examination of serial sections through this caseous focus, the lateral subdivision of the anterior division (plate I, figure 4), coursing towards the posterior half of the focus, became abruptly narrowed and terminated blindly with numerous small pouches lined by a layer of cuboidal epithelial cells. Beyond this point, the lumen was obliterated by connective tissue extending into two branches. The upper one, situated somewhat anteriorly, was transformed into a string of connective tissue in which cartilaginous plates were still demonstrable and merged at the peripheral portion with the connective tissue capsule of the focus (plate I, figure 5). In the lower, somewhat posterior, branch however, only the proximal half was completely obliterated, while in the distal half a centrally situated string of caseated debris was seen, which fused finally with the caseated focus (plate I, figure 6). Another bronchus, representing a branch of the anterior subdivision of the anterior bronchus and coursing towards the anterior half, was completely obliterated by connective tissue containing remnants of mucous glands and bronchial cartilage in the center and at the periphery (plate I, figure 7). The focus itself showed firm caseation throughout and calcium deposits in various areas. It was well walled off by a connective tissue capsule and was occasionally diffusely infiltrated by lymphocytes.

The mechanism of closure in this cavity was one of rapid contraction of the cavity due to relaxation of the lung parenchyma during pneumothorax, accompanied by collapse, approximation, and finally obliteration by connective tissue, of the draining bronchial branches. The process occurred in the entire length of two of the bronchi and at the proximal portion in the third. The distal portion of the latter was filled with caseous material, fusing with the caseous focus proper. As the bronchial occlusion occurred rapidly, large amounts of caseous material of the cavity were retained, thus accounting for the large focus.

The right upper lobe was markedly shrunken, measuring about 8.0 cm. in height, 3.0 cm. in width and about 5.0 cm. in depth. It was enveloped by a moderately thick fibrotic pleura. On cutting this lobe in 1.0 cm. thick layers, a spherical, sharply demarcated, fibrotic scar about 1.0 cm. in diameter was found in the third layer closely underneath and fusing anteriorly with the pleura. The pleura overlying the scar was about 0.5



a-2-33

2-16-35

1

2

3



PLATE II

FIGS. 1, 2, and 3. Case 1 (M. S.) Roentgenograms demonstrating the cavity in the right upper lobe before institution of pneumothorax and its reduction in size and eventual disappearance on this type of treatment.

FIG. 4. Photomicrographs illustrating the different tissue formations in a segment of the stellate focus (figure 3) from the center portions towards the periphery representing the former cavity, on film of February 2, 1933 (figure 1). The central portion, seen at the left, is rich in nuclei and capillaries; this is followed by a fibrillar zone and on the right is a more cellular zone rich in blood vessels.

PLATE I

FIGS. 1 and 2. Case 1 (M. S.) Roentgenograms revealing the cavity in the left upper lobe on film of February 2, 1937 before institution of pneumothorax (figure 1) and its replacement by a dense focus on film of October 19, 1943 (figure 2).

FIG. 3. Coronal section of the left upper lobe through the dense focus representing the posterior half. To the left, the lateral subdivision of the anterior division of the upper lobe bronchus is seen close to the blind end.

FIGS. 4, 5, and 6. Photomicrographs of representative sections of the lateral subdivision and its two branches in which the latter divided with a portion of the posterior half of the focus. Figure 4 illustrates a cross section of the actual lateral subdivision; figure 5 that near the blind end and the obliterated branch (above); and the obliterated proximal portion of the other branch (below) at the branching off point; the distal portion of this branch is filled with caseation (figure 6).

FIG. 7. Photomicrograph of the obliterated branch of the patent anterior subdivision.

FIG. 8. Schematic drawing of the closed cavity and the ultimate picture of the former tributary bronchi.

em. thick, shading off upward and downward. The horizontal subdivision of the apical division terminated at the medial aspect of the scar. In the remaining layers, there were a few small, round, caseous, partially calcified, foci in the summit and anteriorly in the angle formed by the visceral pleura and the obliterated fissure between this lobe and the middle lobe.

On microscopic examination, the scar consisted almost uniformly of collagenous connective tissue circularly arranged and denser at the periphery than at the center. The outermost zone was much less dense and very rich in small blood vessels. The central portions exhibited densely crowded capillaries with plasma cells and lymphocytes between them (plate II, figure 4). One small bronchus coursing along the scar terminated at its medial aspect. It could also be seen that two bronchioles communicated with the surface of the visceral pleura and that one caseous tubercle had ruptured through the pleura, thus accounting for the source of the empyema.

*Summary:* This man had a recent cavity in the right upper lobe and under pneumothorax this cavity gradually shrank concentrically. After the caseous material was simultaneously expelled, the small residual cavity shrank further, finally disappearing completely by formation of a scar. The latter consisted in the outer zone of dense collagenous connective tissue and in the center of loose connective tissue rich in capillaries. The draining bronchus, coursing in its peripheral segment along the scar, terminated blindly at the medial aspect of the latter.

*Case 2:* The patient (T. S.) was a 21-year-old white male. The onset of the disease was in June 1939 and was characterized by a pneumonia in the left lower lobe. From there it spread to the right upper lobe. Pneumothorax was induced on the left side in December 1939, and on the right in March 1940, because of a cavity measuring 2.5 cm. in diameter, situated posterolaterally between the fifth and sixth ribs. After a pneumonolysis in June, the cavity diminished in size and was no longer demonstrable in January 1941. Over the following years it shrank more and more, exhibiting an irregularly outlined opacity on a chest film on June 8, 1945. When the patient was transferred to this hospital in January 1946, two cavities and a bronchopleural fistula were demonstrated on the left side. Thoracoplasty was decided upon after partial re-expansion of both lungs. The posterior segments of the upper six ribs were removed January 30, 1946. The patient died a few hours thereafter in a state of severe anoxemia.

*Postmortem findings:* The right upper lobe was found markedly collapsed by pneumothorax, being pushed toward the mediastinum and backward. In the lower third, however, it extended laterally as a ridge, triangular shaped in the sagittal plane to the chest wall. It was adherent to the latter and at the base to the middle lobe. On cutting the right upper lobe in 1.0 cm. thick layers and on tracing the various bronchi, a lateral branch of the posterior division, coursing somewhat beneath the crest of the ridge, terminated blindly in a double leaf-shaped caseated focus with a calcified center surrounded by a fibrotic capsule. This focus was unquestionably the relic of the cavity observed on the roentgenograms during life. Scattered through the right upper lobe were numerous small foci of recent tuberculous bronchopneumonia.

Histological analysis furnished no more information as to the composition of the focus itself than was obtained on macroscopic examination. It was found, however, that a string of connective tissue which contained remnants of bronchial cartilage coursed first in a straight line and then deviated forward for a short distance, eventually fusing with the blind end of a bronchus.

*Summary:* This patient had a cavity in the right upper lobe, drained by the lateral subdivision of the posterior division of the right main bronchus. Under pneumothorax the upper two-thirds of this lobe collapsed readily. In the lower third of the lobe, where the cavity was situated, relaxation took place only anteriorly and from behind, wedging in the lung parenchyma because of adhesions to the chest wall. A double leaf-shaped folding of the cavity wall resulted and the draining bronchus became deviated forward from its straight course as well. Then, under shrinkage, the caseous content became inspissated with subsequent deposition of calcium. The bronchus, unquestionably involved by tuberculosis at the portion contiguous to the cavity, was included in the contraction and finally became obliterated by fibrillar connective tissue.

*Case 5:* The patient (A. G.) was a 46-year-old white female. The onset of the disease was in 1917 with an hemoptysis. Roentgenographic examination of the chest revealed bilateral apical infiltration. Following bed-rest for five years, her disease became "arrested" in 1922. Thereafter the patient was well until 1933, when the sputum again contained tubercle bacilli. A roentgenogram taken on May 23, 1933, showed a cavity in the left lung at the level of the sixth rib posteriorly. The sputum again became negative for tubercle bacilli on bed-rest of one year's duration. A roentgenogram taken June 30, 1937, revealed a stellate opacity at the site of the former cavity (plate III, figure 1). Because of another hemoptysis on January 12, 1943, and an attack of "congestion of the lung" on March 1, 1943, the patient entered this hospital on September 25, 1943. A roentgenogram taken shortly thereafter revealed bilateral fibrotic disease of the upper lobes with bronchiectasis. The focus seen in 1937 on the left side had decreased in density, appearing much "harder". The sputum, though amounting to 2.5 ounces daily, revealed tubercle bacilli on direct examination only twice after admission, although organisms were occasionally obtained by culture. The patient died October 20, 1944, of right heart failure.

*Postmortem findings:* The upper lobe of the left lung was markedly shrunken, showing fibrosis and crowded sacular and cylindrical bronchiectasis with a small amount of intervening emphysematous parenchyma. The lower lobe was enlarged as a result of diffuse compensatory emphysema. In its posterior half, in the area supplied by the superior division of the lower lobe bronchus, there was a stellate fibrotic scar measuring about 2.0 cm. across and 1.0 cm. in height. In the adjacent parenchyma, the emphysema was much more pronounced forming small blebs between the prongs of the scar.

On microscopic examination of serial sections, the stellate scar (plate III, figure 2) consisted throughout of fibrillar connective tissue interspersed with numerous dilated blood and lymph vessels. At the outer zone, several large arteries exhibited obliterating arteritis. In numerous areas there were foci of lymphocytes, round in the periphery and elongated in the center, extending toward the former draining bronchus. Nowhere was there seen any evidence of tuberculous granulation tissue. The scar was rather thin in the sagittal diameter. It extended almost perpendicular to the course of the tributary bronchus that terminated blindly. This bronchus was lined by a layer of cylindrical epithelial cells. The basement membrane shaded off gradually towards the blind end and finally disappeared completely. At its termination the bronchial lumen showed numerous small pouches beyond which collections of lymphocytes were seen extending into the scar.

*Summary:* This patient had a cavity in 1933. On bed-rest it became completely obliterated by contraction and approximation of its wall, predominantly in an an-



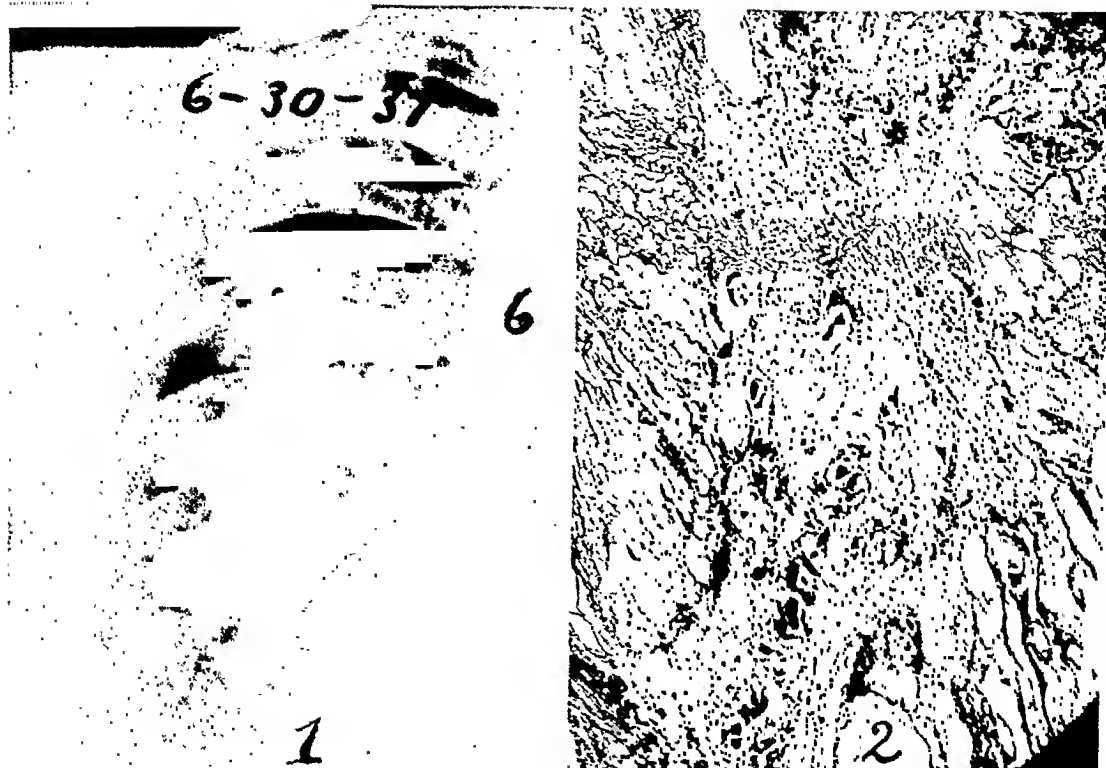


PLATE III

FIG. 1. Case 3 (A. G.) Roentgenogram revealing a stellate opacity at the level of the sixth posterior rib on the left, on film of June 30, 1937, at the site of a cavity which was visible on a film of May 23, 1933.

FIG. 2. Photomicrograph of the stellate scar at the site of the former cavity. Notice the congested, dilated blood and lymph vessels seen within the fibrotic tissue and the emphysematous blebs between the stellate processes of the scar. Near the upper left corner, the blind termination in the scar of the former draining bronchus (superior division of the left lower lobe bronchus) may be seen.

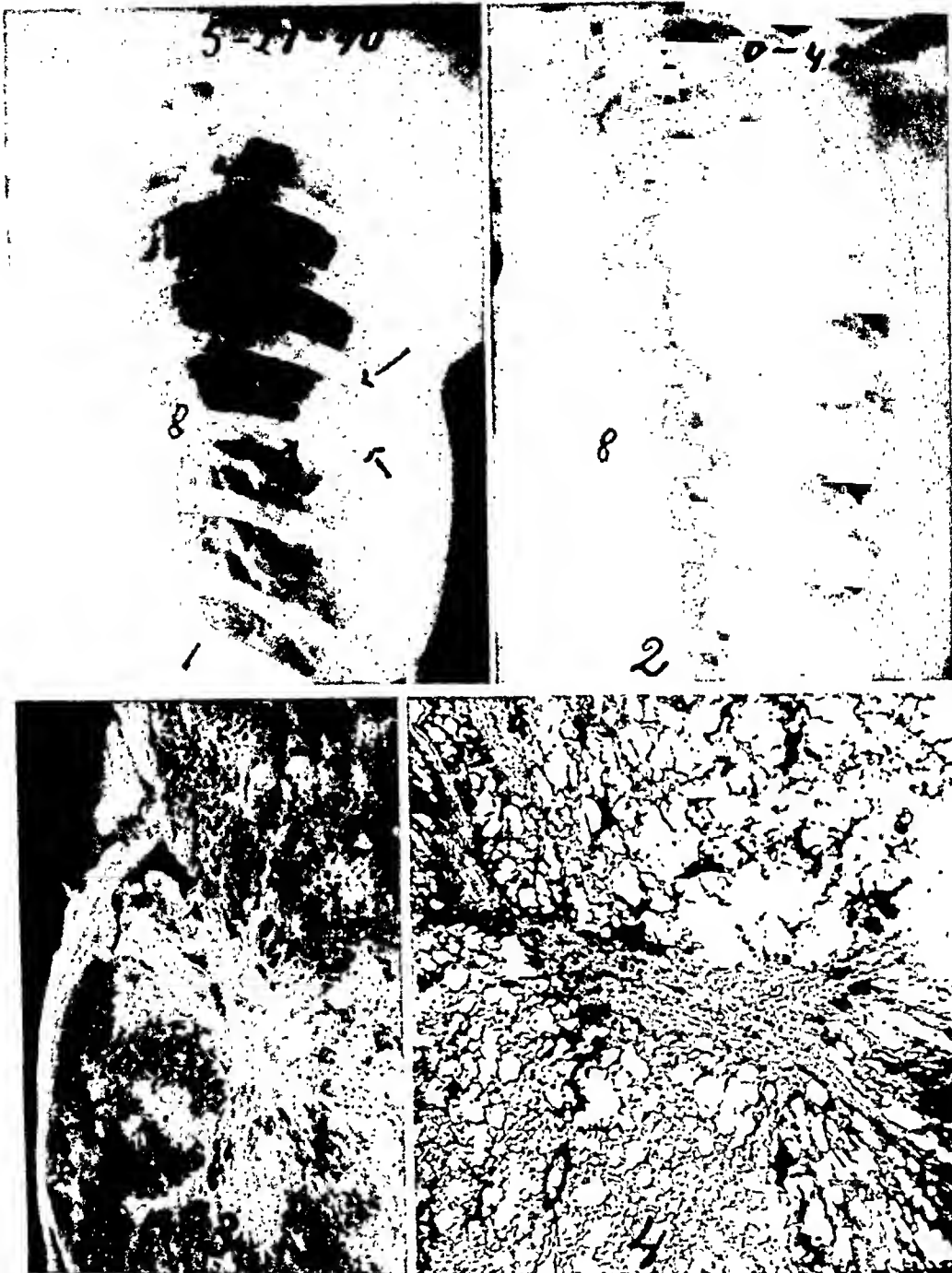


PLATE IV

FIGS. 1 and 2. Case 4 (M. Del G.) Roentgenograms revealing a cavity in the right lower lobe on film of May 27, 1940 (figure 1) before institution of pneumothorax and a stellate opacity after optional re-expansion on film of January 20, 1942 (figure 2).

FIG. 3. Coronal section showing the stellate scar representing the former cavity (figure 1) in the right lower lobe. A few terminal hematogenous tubercles are seen scattered throughout the lung parenchyma. At the left, the fused parietal and visceral pleura, with a portion of an interlobular septum extending towards the scar, is clearly discernible.

FIG. 4. Microscopic section through the stellate scar (figure 3) representing the former cavity in the right lower lobe. Near the left upper corner a small portion of the interlobular septum illustrated in figure 3 is seen. The two bronchioles that terminated blindly at the outer zone of the scar are not visible in this figure.

terior posterior direction. The process apparently took place rather slowly while at the same time the caseous material was completely expelled. Also at the same time, or shortly thereafter, an identical process occurred at the broncho-cavitary communication and resulted finally in its complete occlusion. Presumably the tuberculous granulation tissue lining the cavity wall was very small in amount and was readily absorbed and replaced by fibrotic tissue, with consequent complete healing of the cavity.

*Case 4:* The patient (M. Del G.) was a 20-year-old white female. The onset of the disease, catarrhal in type, was in September 1939. A roentgenogram taken November 21, 1939, after admission to the hospital, showed bilateral infiltration of both lungs above the fifth anterior rib with a cavity measuring  $2.5 \times 4.5$  cm. in the right upper lobe and beginning cavity formation in the right lower lobe at the level of the eighth posterior rib. The latter cavity measured  $2 \times 2$  cm. by May 27, 1940 (plate IV, figure 1). Therapeutic pneumothorax was induced on the right side on July 8, 1940. The pneumothorax was abandoned, however, in September 1940 because of numerous thick bands of adhesions about the upper lobe and the development of an uncontrollable massive effusion. The lung was optionally re-expanded by September 26, 1941. A roentgenogram taken at this time showed an oval-shaped faint opacity, not sharply demarcated and about 1.0 cm. across, at the site of the former cavity in the right lower lobe. During the subsequent months and years this opacity steadily decreased in density and its outline became jagged (plate IV, figure 2). In the meantime, the disease progressed on the left, where a huge cavity had also formed. As any type of active therapy was considered ineffective, the patient was kept only under nursing care. She died March 16, 1945.

*Postmortem findings:* On cutting the right lower lobe in 1.0 cm. thick layers, a scar was found about 2.0 cm. underneath the pleura, in about the middle layer, supplied by a branch of the lateral division of the lower lobe bronchus. The scar had a stellate outline, measured about 1.0 cm. across, and was of a whitish leathery-like consistency (plate IV, figure 3). On microscopic examination, it had the stellate configuration as seen macroscopically. The scar consisted almost throughout of fibrillar connective tissue, somewhat denser at the periphery. The central portions contained numerous thin walled, dilated blood and lymph vessels. In several areas the connective tissue structures were interspersed with collections of lymphocytes (plate IV, figure 4). Nowhere was there seen any trace of residual tuberculous tissue. Two bronchioles terminated blindly, one at the outer zone of the scar and the other somewhat away but connected with the latter by a fibrotic string.

*Summary:* The cavity was located at the periphery of the lower lobe and was supplied by two bronchioli of the lateral division. The cavity had formed in a short time and was therefore thin walled. On institution of pneumothorax, it collapsed readily. In this process of collapse, two draining bronchioli were included, the lumens of which finally became obliterated in the segment close to the cavity wall. As the cavity had formed rapidly, due to liquefaction of the caseous material, the latter was readily expelled. The wall of the collapsed cavity was rapidly replaced by fibrotic tissue which also simultaneously obliterated the lumen.

#### DISCUSSION

The mechanism at work resulting in the disappearance of the cavities by conversion into closed caseous foci or by healing was the same in this series of

five instances as had been previously reported (1). There was no difference whether the cavity was of recent development and thin walled or of long standing and with a rather thick wall. It is obvious that closure will take place in a much shorter time in the former than in the latter under favorable conditions, that is, when the pleural space is free and when the cavity is surrounded by normal lung parenchyma. Under pneumothorax, however, it is known from experience that the length of time required for closure can be determined to a great extent by the clinician's measurements of the amount of air instilled and the interval at which air is given. The clinician usually notices with satisfaction the rapid decrease in the size of the cavity and its final closure under this type of treatment and the patient is full of joy on hearing this news. Yet such jubilation is only partially justified, as shown by a careful analysis of the end results of the series previously reported (1) and the present one. The two series represent in the majority of cases only closed cavities which were transformed into caseous inspissated foci, though well walled off. Such foci persist probably for the rest of the patient's life; in other words, for many years or decades if the patient lives that long. The caseous foci contain varying amounts of calcium deposits, depending for the most part on the lapse of time and to some extent on the size of the foci. In larger ones the calcium is usually found at the periphery, in the smaller ones in the center. Though these inspissated foci may shrink in the course of years, complete healing, that is, their replacement by a scar formed by connective tissue growing in from the capsule with simultaneous absorption of the caseous material, probably takes place very rarely and only in the small foci, if it occurs at all.

It may be seen in table 1 that, in the combined series, closed foci were encountered in seven out of eight instances treated by pneumothorax. After cavity closure was observed on the roentgenogram, closed foci were still present at four years and eight months in cases 2 and 3 of the previously reported series, and at six years and eight months and at five years, respectively, in cases 1 and 2 of the present series (table 1). In the latter instances the original cavities were only moderate in size, measuring 4.0 cm. and 2.5 cm. in diameter, respectively. The time in which closure was achieved ranged in all these cases from six to eight months. The cavity was observed to close in a comparable period in case 5 of the previous series, where the patient was treated on bed-rest alone. Upon inquiry as to the cause for the development of these closed foci, it seems reasonable to assume that the above mentioned time in which closure was attained was much too short for complete sloughing off and expulsion of caseous material and cleansing of the lining of the cavity.

In this connection, it should be pointed out that in some cavities, especially those formed in recent bronchogenic infiltrates, large amounts of caseous material can not only be retained, but some of it may even be squeezed into the draining bronchus or bronchi for some distance when the lung is rapidly collapsed. Thus these cavities may disappear, but they do not always become converted into closed foci. As they are only plugged, they are apt to reopen after removal of the plug, as is frequently seen during an upper respiratory infection or violent coughing or during re-expansion.

The sloughing off and expulsion of caseous material and cleansing of the cavity

TABLE 1  
Final status of cavity determined postmortem

| CASE  | AGE OF CAVITY            | DIMENSIONS OF CAVITY | LAPSE OF TIME UNTIL CLOSURE OF CAVITY WAS OBSERVED IN THE ROENTGENOGRAM | LENGTH OF TIME AFTER CLOSURE WAS OBSERVED IN THE ROENTGENOGRAM | FINAL STATUS OF CAVITY        |
|---|--------------------------|----------------------|---|--|-------------------------------|
| Case 1, M. S. (left lung)<br>Feb. 1937<br>*Aug. 16, 1937<br>May 17, 1944                | 1½ yrs. old              | 4.0 cm.              | About 6 months  | 6 years 8 months   | Closed, partially calcified   |
| Case 2, T. S.<br>March 1940<br>June 1940 (pneumonolysis)<br>*June 1941<br>June 30, 1946 | Recent                   | 2.5 cm.              | 8 months  | 5 years  | Closed, partially calcified   |
| Case 1, r., M.S. (right lung)<br>April 1933<br>*June 1934<br>May 17, 1944               | Recent                   | 3.0 cm.              | 14 months   | About 10 years   | Healed                        |
| Case 3, A. G.<br>May 23, 1933<br>*July 1934<br>1944                                     | Recent                   | 2.5 cm.              | 14 months   | 10 years   | Healed                        |
| Case 4, M. Del. G.<br>July 8, 1940<br>*Sept. 26, 1941<br>March 6, 1945                  | Recent                   | 2.0 cm.              | 14 months   | 3 years 5 months   | Healed                        |
| CASES PREVIOUSLY REPORTED;<br>AM. REV. TUBERC., 1944, 50, 500                           |                          |                      |   |  |                               |
| Case 1, C. B.<br>Oct. 23, 1936<br>*July 24, 1937<br>Nov. 28, 1938                       | Recent                   | 2.0 cm.              | 8 months  | 1 year 4 months  | Closed, fine calcium granules |
| Case 2, G. D. K.<br>July 6, 1936<br>*Jan. 23, 1937<br>Oct. 6, 1941                      | Moderately long standing | 4.5 cm.              | 7 months  | 4 years 8 months   | Closed, fine calcium granules |
| Case 3, S. G.<br>Dec. 1935<br>*May 1937<br>Jan. 11, 1942                                | Long standing            | 7.5 x 5.0 cm.        | 1 year 6 months   | 4 years 7 months   | Closed, fine calcium granules |

TABLE 1—Continued

| CASE  | AGE OF CAVITY | DIMENSIONS OF CAVITY | LAPSE OF TIME UNTIL CLOSURE OF CAVITY WAS OBSERVED IN THE ROENTGENOGRAM | LENGTH OF TIME AFTER CLOSURE WAS OBSERVED IN THE ROENTGENOGRAM | FINAL STATUS OF CAVITY        |
|---|---------------|----------------------|---|--|-------------------------------|
| Case 4, L. S. 2×<br>May 10, 1937<br>*Feb. 21, 1938<br>Dec. 27, 1938 | Recent        | 1.5 cm.              | 9 months  | 10 months  | Closed, fine calcium granules |
| Case 5, G. B.<br>Nov. 12, 1942<br>*Aug. 2, 1943                     | Recent        | 3.0 cm.              | 8 months  | 8 months   | Closed                        |

\* Italicized date represents the date on which closure of the respective cavity was observed for the first time in the Roentgenogram after treatment was instituted, represented by the first date. The third date indicates end of observation.

lining had apparently occurred in case 1 on the right side and in cases 3 and 4 of the present series in which the cavities had completely healed. The time until closure was observed was much longer, being about fourteen months in each case. In case 3 closure occurred on bed-rest; and in the others after pneumothorax, which in one was replaced by a pleural effusion during optional re-expansion. This relation of the time of apparent closure to healing is most clearly demonstrated in the end results of case 1, with cavities in both upper lobes. Although the character, the size and the type of treatment (pneumothorax) of the original cavities were about identical, the right lung cavity was found completely healed ten years after closure. This healed cavity and the cavities of cases 3 and 4 (treated on bed-rest) were roentgenographically demonstrable for a fourteen month period before apparent closure. The time within which healing had taken place after closure cannot be stated definitely. It will unquestionably depend on such factors as size; location, and age of the cavity; thickness and character of the wall; and the influence exerted by the contracting forces, whether concentrically or predominantly in one direction. Small amounts of necrotic tissue will probably be retained even under the most favorable conditions, but this will be absorbed gradually by ingrowing connective tissue replacing the tuberculous inner layers of the cavity wall. Under continuous regression with the granulation tissue becoming poor in nuclei but rich in fibres, a bland scar is ultimately formed with a main outline, either spherical or elongated, and with stellate processes extending from its outer zone.

#### SUMMARY

1. Five additional instances of anatomical disappearance of tuberculous cavities confirming previous observations on the mechanism involved are reported.

2. Two cavities in the series were converted into closed inspissated foci con-

taining varying amounts of calcium deposits. These lesions had been treated by pneumothorax. Three cavities had completely healed; one under pneumothorax, the second on bed-rest, and the third on bed-rest after the cavity had disappeared under a short-term pneumothorax.

3. The length of time of observation after disappearance of the cavities from the roentgenogram was six years, eight months, and five years, respectively, in the two instances with closed inspissated foci. In the three instances with healed cavities, the period of observation after apparent closure was ten years in two cases, and three years and five months in the third.

4. The factors leading to the two types of end results in the present and in a previously reported series are discussed.

#### SUMARIO

##### *Cierre y Cicatrización de las Cavernas Tuberculosas*

1. Comunicáanse cinco casos más de desaparición anatómica de cavernas tuberculosas que confirman previas observaciones relativas al mecanismo participante.

2. Dos cavernas de la serie se convirtieron en focos espesados cerrados que contenían cantidades variables de depósitos de calcio. Esas lesiones habían sido tratadas con el neumotórax. Tres cavernas habían cicatrizado completamente: una con el neumotórax; otra con el encamamiento, y la tercera con el reposo en cama después de desaparecer la caverna tras un neumotórax de poca duración.

3. El período de observación consecutivo a la desaparición de las cavernas, de la radiografía, duró seis años y ocho meses, y cinco años, respectivamente, en los dos casos con focos espesados obturados. En los tres casos de cavernas cicatrizadas, la observación consecutiva al cierre aparente duró diez años en dos casos y tres años y cinco meses en el otro.

4. Discútnense los factores que condujeron a las dos formas de resultados terminales en la serie actual y en otra anterior.

#### *Acknowledgment*

The writer wishes to express his appreciation to Doctor Harry Golembe and Doctor Joseph Grund of Liberty, New York, for furnishing the roentgenograms of the early disease of cases 1 and 3, respectively.

#### REFERENCE

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# DRUG-RESISTANT TUBERCLE BACILLI IN PATIENTS UNDER TREATMENT WITH STREPTOMYCIN<sup>1,2,3,4,5</sup>

E. WOLINSKY, A. REGINSTER<sup>6</sup> AND W. STEENKEN, JR.<sup>7</sup>

Attention was first called to the appearance of streptomycin-resistant tubercle bacilli in patients treated with streptomycin by Youmans et al. (1) in 1946. Steenken (2, 3), Youmans and Karlson (4), and Karlson, Feldman and Hinshaw (5), followed with further reports on the subject. Recently, McDermott, Muschenheim and their collaborators (7, 8) and the Veterans Administration Streptomycin Committee (9) published data on the sensitivity of cultures isolated from their patients at frequent intervals. Pyle (6), in her studies on drug-resistant tubercle bacilli, reported the results which she obtained by planting sputa directly on solid medium containing various concentrations of streptomycin.

The present paper consists of a report of the results of streptomycin sensitivity tests on tubercle bacilli isolated at weekly intervals from a large group of patients before, during, and after, treatment with various doses of the drug. The rate at which drug-resistance appears, as well as the degree of resistance manifested, and its permanence after therapy is discontinued, will be presented.

## METHODS

Tubercle bacilli were recovered from sputum, gastric contents, urine, or pleural fluid by the conventional method of digestion and concentration with sodium hydroxide. The organisms were then cultured on a modified tentative medium<sup>8</sup> recommended by the Committee on Evaluation of Laboratory Procedures of the American Trudeau Society (10). These cultures were examined weekly, and, as soon as the first sign of growth appeared (from twelve to twenty-two days with highly positive sputa), it was transferred to a tube of Tween-albumin liquid medium<sup>9</sup> (11). Individual colonies in the same culture tube may occasionally give different results when tested for sensitivity, and for this reason a representative sample of many colonies was used when the growth was

<sup>1</sup> From the Trudeau Laboratory of The Trudeau Foundation for the Clinical and Experimental Study of Pulmonary Disease, Trudeau, New York.

<sup>2</sup> This study is part of the Streptomycin-Tuberculosis Research Project of the American Trudeau Society, Medical Section, National Tuberculosis Association. The drug was generously donated to the Society by Abbott Laboratories, Eli Lilly and Company, Merck and Company, Inc., Charles Pfizer and Company, Inc., E. R. Squibb and Sons, and The Upjohn Company.

<sup>3</sup> This study was aided by grants from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service.

<sup>4</sup> Portions of this study were presented at the Third Streptomycin Conference of the Veterans Administration, sponsored by the National Research Council, St. Louis, May 1947.

<sup>5</sup> Parts of this paper were presented at the Forty-eighth General Meeting of the Society of American Bacteriologists, Minneapolis, May 1948.

<sup>6</sup> Research Fellow of The Trudeau Foundation, from the University of Liege, Belgium, Department of Prof. L. Brull.

<sup>7</sup> With the technical assistance of Marjorie M. Smith, Verna Wetzel and Barbara O'Neil.



transferred to the liquid medium. If only a single colony appeared, this was transferred and tested as usual.

Streptomycin sensitivity tests were done essentially as described previously (12). Briefly, 0.1 cc. of a seven- to ten-day smoothly-growing culture in Tween-albumin medium was inoculated into a series of tubes of the same liquid medium (pH 7.0 to 7.1) containing concentrations of 0.5, 1.0, 2.5, 5, 10, 15, 30, 60, 125, 250, 500, and 1,000 mcm. of streptomycin per cc. This series of tubes was examined at frequent intervals for fourteen days. Those which exhibited an increasing turbidity by the fourteenth day were considered positive for growth, all others negative. The sensitivity was recorded as the lowest concentration of streptomycin which inhibited growth. Any doubtful results were repeated.

*Estimation of Approximate Proportion of Resistant Organisms:* When a strain of tubercle bacilli manifests resistance to streptomycin, not all the organisms in the culture are necessarily drug-fast. Therefore, it is important to know what percentage of the microorganisms in a culture must be resistant to the drug in order to give a result of "resistant" in the sensitivity test. An approximate estimate of this proportion may be determined by observing the lag period before turbidity appears in a given concentration of streptomycin. To illustrate: Artificial mixtures containing various proportions of two strains of H37 Rv microorganisms, one sensitive and one resistant to the drug, were prepared. One strain was made resistant *in vitro* by serial subculture in Tween-albumin medium containing gradually increased concentrations of streptomycin until the organisms were able to grow well in medium containing 1,000 mcm. per cc. The other strain was sensitive to less than 0.5 mcm. per cc. In table 1 may be seen what occurs when such mixtures are subjected to the routine sensitivity test.

In order to show growth in 1,000 mcm. per cc. by the fourteenth day (when the final readings were made), the mixture had to contain approximately 0.1 per cent resistant organisms. The duration of the lag period was inversely related to the relative number of drug-resistant bacilli. A comparison of the results obtained in these experiments with the Tween-albumin medium and the serum-synthetic medium described by Youmans (4) are also presented in table 1. There was no significant difference demonstrable in these results. When the mixtures

<sup>8</sup> Formula:

Egg yolk—500 cc.  
Potato water (8 per cent glycerin)—333 cc.  
Malachite green—1:10,000

<sup>9</sup> Formula:

|   |              |
|---|--------------|
| KH <sub>2</sub> PO <sub>4</sub>                       | 1.0 gram     |
| Na <sub>2</sub> HPO <sub>4</sub> :12 H <sub>2</sub> O | 6.25 "       |
| Sodium citrate—2 H <sub>2</sub> O                     | 1.5 "        |
| MgSO <sub>4</sub> :7 H <sub>2</sub> O                 | 0.6 "        |
| Asparagin   | 0.2 per cent |
| Glucose   | 0.2 " "      |
| Vegex   | 0.02 " "     |
| Tween 80  | 0.02 " "     |
| Bovine Albumin  | 0.5 " "      |
| Distilled H <sub>2</sub> O to make 1,000 cc.          |              |

in Tween-albumin medium were incubated for seven days before being tested, the results were the same as those presented in the table, suggesting that the growth rates of the sensitive and resistant organisms were about the same.

Thus, it is possible to estimate the relative number of resistant organisms in a culture by observing the lag period before growth appears; in other words, a cul-

TABLE 1

*Sensitivity to streptomycin of artificial mixtures of drug-sensitive and drug-resistant tubercle bacilli*

| MIXTURE   | SIZE OF INOC. INTO EACH TUBE |                          | MEDIUM                                     | RESULT OF SENSITIVITY TEST AS READ ON 14TH DAY                                | NUMBER OF DAYS BEFORE GROWTH APPEARED IN 1,000 MCM. PER CC. |
|---|------------------------------|--------------------------|--|---|---|
|   | Approx. no. sens. org.       | Approx. no. resist. org. |  |   |   |
| 100 per cent resist.                              | 0                            | 7,000,000                | Tween-alb 1                                | Over 1,000 mcm. per cc.   | 4-6   |
| 60 per cent resist.<br>40 per cent resist.        | 2,800,000                    | 4,200,000                | Tween-alb 1                                | Over 1,000 mcm. per cc.   | 5-6   |
| 40 per cent resist.<br>60 per cent sens.          | 4,200,000                    | 2,800,000                | Tween-alb 1                                | Over 1,000 mcm. per cc.   | 6   |
| 20 per cent resist.<br>80 per cent sens.          | 5,600,000                    | 1,400,000                | Tween-alb 1                                | Over 1,000 mcm. per cc.   | 7   |
| 10 per cent resist.<br>90 per cent sens.          | 6,300,000                    | 700,000                  | Tween-alb 1                                | Over 1,000 mcm. per cc.   | 8   |
| 1 per cent resist.<br>99 per cent sens.           | 6,930,000                    | 70,000                   | Tween-alb 1<br>Tween-alb 2<br>Serum-Synth. | Over 1,000 mcm. per cc.<br>Over 1,000 mcm. per cc.<br>Over 1,000 mcm. per cc. | 11-12<br>11<br>10   |
| 0.1 per cent resist.<br>99.9 per cent sens.       | 6,993,000                    | 7,000                    | Tween-alb 2<br>Serum-Synth.                | Over 1,000 mcm. per cc.<br>Over 1,000 mcm. per cc.                            | 14-16<br>14-15  |
| 0.01 per cent resist.<br>99.99 per cent sens.     | 6,999,300                    | 700                      | Tween-alb 2<br>Serum-Synth.                | 0.5 mcm. per cc.<br>1.0 mcm. per cc.  | 17-10<br>17-19  |
| 0.001 per cent resist.<br>99.999 per cent sens.   | 6,999,930                    | 70                       | Tween-alb 2<br>Serum-Synth.                | 0.5 mcm. per cc.<br>0.5 mcm. per cc.  | 20-22<br>20-22  |
| 0.0001 per cent resist.<br>99.9999 per cent sens. | 6,999,993                    | 7                        | Tween-alb 2<br>Serum-Synth.                | 0.5 mcm. per cc.<br>0.5 mcm. per cc.  | Over 21 days<br>Over 21 days                                |
| 100 per cent sens.                                | 7,000,000                    | 0                        | Tween-alb 1                                | 0.5 mcm. per cc.  | No growth   |

Tween-alb 1 = 0.05 per cent Tween 80 + 0.2 per cent albumin. Tween-alb 2 = 0.02 per cent Tween 80 + 0.5 per cent albumin.

Results of streptomycin sensitivity tests in liquid media of prepared mixtures of H37 Rv microorganisms sensitive to streptomycin, and H37 Rv microorganisms made resistant to 1,000 mcm. per cc. of streptomycin.

ture which produces growth in the tube containing 1,000 mcm. of streptomycin per cc. of medium in four or five days may be considered to contain a majority of organisms resistant to 1,000, whereas a culture which shows growth in this tube only after twelve to fourteen days of incubation may be considered to have less than 1 per cent of its population actually resistant to 1,000 mcm. per cc. of medium.

## RESULTS

## Patients at Trudeau Sanatorium

This report is based on the study of 47 patients at Trudeau Sanatorium who were treated for periods of six to sixteen weeks. All 47 were treated for at least six weeks, 33 were treated for at least eight weeks, 24 for ten weeks, 20 for twelve weeks, 13 for fourteen weeks, and 8 for sixteen weeks. The dosage of streptomycin varied from 2.0 grams daily, with injections every four hours, to 0.5 grams once a day, but the majority of the patients received 1.0 gram a day in two injections. Cultures of sputum, gastric contents, urine, or pleural fluid were made weekly during treatment, and monthly thereafter.

All patients produced cultures that were sensitive to 0.5 mcm. of streptomycin per cc. before therapy was started. Of the 47, there were 8 who yielded drug resistant<sup>10</sup> tubercle bacilli during treatment. The earliest resistant culture was isolated from a patient on the twenty-ninth day of therapy, and these organisms were resistant to the action of 1,000 mcm. of streptomycin per cc. Other drug-resistant cultures isolated early in the course of treatment were first obtained on the thirtieth, the thirty-fourth, and the thirty-sixth day. The other four drug-resistant strains were obtained after six, seven, eight, and eleven weeks of therapy.

In table 2 are presented the results of the weekly sensitivity tests, based on the number of patients with positive cultures for each week. The percentage of positive cultures that were resistant to 10 or more mcm. per cc. is given in the next to last horizontal column.

It will be observed that there were no drug-resistant cultures isolated during the first three weeks of therapy. After four weeks, however, two cultures, or 4.5 per cent of the positive cultures, proved to be resistant. This percentage rose steadily from week to week as treatment continued.

The degree of resistance manifested by these cultures varied widely. Four of the 8 patients yielded organisms which grew readily in 1,000 mcm. per cc.; two cultures increased in resistance up to 125 to 250 mcm. per cc. and remained at that level despite the continuance of treatment; two cultures increased up to 15 to 30 mcm. per cc. and no higher. At the end of six weeks of therapy, 75 per cent of the positive cultures were still sensitive to 1.0 mcm. per cc. or less. At the end of twelve weeks, only 58 per cent of the positive cultures exhibited this same degree of sensitivity.

*Miscellaneous Observations:* In addition to the group of patients already mentioned, sensitivity tests were done on many patients under treatment by their private physicians in Saranac Lake. Because of the great variation in dosage, length of treatment, and interval between cultures, it is impossible to present a complete analysis of this group. There were 98 patients, however, on whom sufficient data were available to determine whether or not they had produced drug-resistant cultures during therapy. Adding these 98 patients to the group al-

<sup>10</sup> In this report, cultures resistant to 10 or more mcm. per cc. are considered "drug-resistant."

ready described, gives a total of 145 patients whose cultures were tested for sensitivity to streptomycin in this laboratory. Disregarding the dosage and length of treatment (except that each patient was treated for at least four weeks), there were 51, or 35.1 per cent, whose organisms became drug-resistant at some time during therapy, and there were 94, or 64.9 per cent, whose cultures either became negative or remained sensitive.

*Permanence of Resistance:* Tubercle bacilli that are made resistant to streptomycin *in vitro* retain this characteristic for at least a year when cultured in the absence of the drug. Also, a highly resistant H37 Rv strain that has had

TABLE 2

*Sensitivity to streptomycin of tubercle bacilli isolated from patients under treatment with streptomycin at Trudeau*

| MCM. OF STREPTOMYCIN PER CC. OF MEDIUM NECESSARY TO INHIBIT GROWTH | BEFORE TREATMENT |          | AFTER 2 WEEKS |          | AFTER 3 WEEKS |          | AFTER 4 WEEKS |          | AFTER 5 WEEKS |          | AFTER 6 WEEKS |          | AFTER 7 WEEKS |          | AFTER 8 WEEKS |          | AFTER 10 WEEKS |          | AFTER 12 WEEKS |          |
|--|------------------|----------|---------------|----------|---------------|----------|---------------|----------|---------------|----------|---------------|----------|---------------|----------|---------------|----------|----------------|----------|----------------|----------|
|  | Number           | Per cent | Number        | Per cent | Number        | Per cent | Number        | Per cent | Number        | Per cent | Number        | Per cent | Number        | Per cent | Number        | Per cent | Number         | Per cent | Number         | Per cent |
| 0.5 or less  | 43               | 100      | 46            | 100      | 39            |          | 32            |          | 26            |          | 26            |          | 21            |          | 14            |          | 12             |          | 8              |          |
| 0.6-1.0  |                  |          |               |          | 5             |          | 6             |          | 4             |          | 4             |          | 1             |          | 2             |          | 2              |          | 3              |          |
| 2.0-5.0  |                  |          |               |          |               |          | 4             |          | 4             |          | 5             |          | 4             |          | 4             |          |                |          | 1              |          |
| 10-31.2  |                  |          |               |          |               |          | 1             |          | 2             |          | 2             |          |               |          |               |          |                |          | 1              |          |
| 60-125   |                  |          |               |          |               |          |               |          |               |          | 1             |          | 2             |          | 2             |          | 2              |          | 2              |          |
| 250-1,000  |                  |          |               |          |               |          |               |          |               |          |               |          |               |          |               |          |                |          |                |          |
| Over 1,000   |                  |          |               |          |               |          | 1             |          | 2             |          | 2             |          | 3             |          | 4             |          | 4              |          | 4              |          |
| Total 1.0 or less.....   | 43               | 100      | 46            | 100      | 44            | 100      | 38            | 90.5     | 30            | 79       | 30            | 75       | 22            | 71       | 16            | 61       | 14             | 70       | 11             | 58       |
| Total 5.0 or less.....   | 43               | 100      | 46            | 100      | 44            | 100      | 42            | 95.5     | 34            | 89.5     | 35            | 87.5     | 26            | 84       | 20            | 77       | 14             | 70       | 12             | 63       |
| Total 10 or more.....  | 0                |          | 0             |          | 0             |          | 2             | 4.5      | 4             | 10.5     | 5             | 12.5     | 5             | 16       | 6             | 23       | 6              | 30       | 7              | 37       |
| Total positive cultures.....                                       | 43               |          | 46            |          | 44            |          | 44            |          | 38            |          | 40            |          | 31            |          | 26            |          | 20             |          | 19             |          |

monthly testicle passage from guinea pig to guinea pig over a period of eight months still retains this same high degree of resistance. Clinically, streptomycin resistance is likewise relatively permanent. The writers have under observation many patients who yielded tubercle bacilli resistant to 1,000 mcm. per cc. during therapy, and who still produce cultures of equal resistance six to twelve months later. Two patients, who finished their courses of streptomycin with cultures sensitive to 125 to 250 mcm. per cc., still yielded organisms of the same sensitivity twelve months and six months later. This occurred in one of these patients despite the administration of a second course of streptomycin therapy. Many patients, whose cultures exhibited a sensitivity of 2.5 mcm. per cc. after

treatment, still produced cultures of identical sensitivity many months after the drug was discontinued.

Two patients have been observed, however, whose cultures reverted from resistant to sensitive. One yielded cultures resistant to 1,000 mcm. per cc. at the end of his first month of treatment, and equally resistant cultures monthly during his four-month course of therapy and the first month thereafter. Three months later, this patient's sputum culture was again completely sensitive, and since then it has remained sensitive on repeated examination. The other patient produced a culture on the thirty-fourth day of treatment which required from 10 to 15 mcm. per cc. to inhibit its growth. A culture isolated one week later, corresponding to the conclusion of treatment, was sensitive to 2.5 mcm. per cc. The next culture, taken one month later, was also sensitive to 2.5. Organisms isolated three months after therapy were again completely sensitive to 0.5 mcm. per cc. It is not meant to imply that these organisms actually reverted from resistant to sensitive, but the percentage of resistant forms in the culture certainly decreased to a point where they were no longer detectable by the method in use.

One patient has also been observed who finished his forty-two-day course of drug therapy with tubercle bacilli still sensitive to 0.5 mcm. per cc., but who yielded a culture resistant to 30 mcm. per cc. two months later. This was confirmed the month following, when his culture was again moderately resistant. There was no change in the clinical course of the patient's pulmonary tuberculosis, which was one of slow, steady improvement, coinciding with the appearance of the resistant organisms.

#### DISCUSSION

It has been brought out by others (2), and confirmed in this laboratory, that the results of sensitivity tests on a given culture may vary, depending on the composition of the medium used to perform the test. Also, a slight variation may be expected as a result of individual differences in technique in different laboratories. If, however, the method employed remains constant, the results of serial tests performed in a single laboratory, as reported in this paper, should be significant.

For statistical purposes, those cultures which were able to grow in 10 mcm. or more of streptomycin per cc. of medium have been arbitrarily designated as resistant. The choice of this particular concentration (10 mcm. streptomycin per ml.) was influenced by the results of streptomycin therapy in guinea pigs previously infected with cultures of intermediate resistance isolated from patients under treatment (14). It was found that animals infected with cultures sensitive to 5 to 15 mcm. per cc. exhibited a varied response to therapy; some responded well, others responded not at all. Animals infected with all cultures requiring 30 or more mcm. per cc. for inhibition of growth did not respond to treatment; whereas, those infected with most cultures sensitive to 2.5 mcm. per cc., or less, responded well.

The clinical significance of *in vitro* drug-resistance of a patient's tubercle bacilli must be evaluated as soon as possible if streptomycin is to be accorded its proper place in the treatment of tuberculosis. When drug-resistant strains are disseminated by personal contact, will the use of streptomycin become increasingly ineffective? What damage to the patient may be done if therapy is continued in the presence of drug-resistant organisms? Does the fact that a culture is resistant *in vitro* signify that continued treatment with the drug is useless? Careful correlation between laboratory results and the clinical course of the patient's disease is necessary to answer these questions. Some data have already been gathered. There have been many cases of relapse or spread of disease during therapy, coinciding with the appearance of drug-resistant organisms (7, 8, 13). The results of retreatment with streptomycin in patients harboring drug-resistant tubercle bacilli have not been encouraging (7, 8, 13). In the animal body, it is quite definite that guinea pigs and mice infected with drug-resistant tubercle bacilli do not respond to adequate therapy with streptomycin (14, 15, 16) in contrast to the favorable results in animals infected with drug-sensitive organisms.

Until a more effective method is devised to eliminate drug resistance, it would appear that, if it is desired to restrict the production of streptomycin-resistant strains of tubercle bacilli, the best plan is to limit a course of treatment with the drug to four or six weeks, at which time about 75 per cent of positive cultures may be expected to be still sensitive.

#### SUMMARY

1. Cultures of tubercle bacilli recently isolated from 47 patients before treatment with streptomycin were uniformly sensitive to 1.0 mcm. per cc. or less of the drug.

2. Tubercle bacilli resistant to the action of 10 mcm. of streptomycin per cc. or more were found commonly in patients under streptomycin therapy.

3. A drug-resistant culture was isolated as early as twenty-nine days after therapy was begun.

4. The longer treatment was continued, the greater the percentage of patients yielding drug-resistant cultures.

5. Out of a total of 47 patients studied intensively, the percentage of those yielding positive cultures whose organisms were resistant to streptomycin was: 4.5 per cent after four weeks of therapy, 12.5 per cent after six weeks, 23 per cent after eight weeks, and 37 per cent after twelve weeks.

6. An estimate of the relative number of drug-resistant organisms in a culture may be made by noting the lag period before growth appears in the tubes containing streptomycin. The duration of the lag period is inversely proportional to the percentage of resistant organisms.

7. In general, streptomycin resistance is a relatively long-lasting characteristic of tubercle bacilli, both *in vitro* and *in vivo*. The serial cultures from two patients, however, reverted from drug-resistant to drug-sensitive.

## SUMARIO

*Bacilos Tuberculosos Farmacorresistentes en Enfermos bajo Tratamiento con la Estreptomicina*

1. Los cultivos de bacilos tuberculosos recién aislados de 47 enfermos antes de recibir la estreptomycinoterapia mostráronse invariablemente sensibles a 1.0 mcm. o por cc. de la droga.

2. En los enfermos en vías de tratamiento con la estreptomicina encontráronse comúnmente bacilos tuberculosos resistentes a la acción de 10 mcm. o más de estreptomicina por cc.

3. Ya a los 29 días de iniciar el tratamiento se aisló un cultivo farmacorresistente.

4. Mientras más duró el tratamiento, mayor fué el porcentaje de enfermos en que se hallaron cultivos farmacorresistentes.

5. Del total de 47 enfermos estudiados a fondo, el porcentaje que mostró microbios estreptomycinorresistentes entre los de cultivos positivos fué: 4.5 al cabo de cuatro semanas de terapéutica, 12.5 al cabo de seis semanas, 23 al cabo de ocho semanas, y 37 al cabo de doce semanas.

6. Puede calcularse el número relativo de microbios farmacorresistentes en un cultivo observando el período de retardo antes de que aparezcan colonias en los tubos que contienen estreptomicina. La duración del período de retardo se halla en razón inversa al porcentaje de microbios resistentes.

7. En general, la estreptomycinorresistencia es una característica relativamente duradera de los bacilos tuberculosos, tanto *in vitro* como *in vivo*. Sin embargo, los cultivos seriados de dos enfermos viraron de farmacorresistentes a farmacosensibles.

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# STREPTOMYCIN RESISTANT TUBERCLE BACILLI

## Incidence in Patients Treated with Streptomycin

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### INTRODUCTION

Streptomycin resistant tubercle bacilli<sup>4</sup> have been encountered frequently by the many investigators (1, 2, 3, 4, 5) who have studied the tuberculostatic activity of streptomycin. Such tubercle bacilli, having the capacity for growth in high concentrations of streptomycin, have been demonstrated *in vitro* by serial subculture in media containing increasing concentrations of streptomycin; and they have also been identified in the cultures of the exudates of patients who have been treated with streptomycin. Whatever the mechanism of the development of resistant tubercle bacilli may be, these resistant forms have become increasingly important in the treatment of tuberculosis with streptomycin, a chronic disease which ideally requires an extended period of suppressive antimicrobial therapy. Observations thus far have suggested that tubercle bacilli resistant to streptomycin *in vitro* are also resistant to streptomycin *in vivo*. Thus, experimental animals inoculated with tubercle bacilli resistant to streptomycin *in vitro* have failed to respond to treatment with streptomycin (6, 7, 8). There is also evidence (1, 5) that patients whose organisms have become resistant to streptomycin *in vitro* may cease to react favorably, or indeed, may have exacerbations of disease upon continued administration of streptomycin. In addition, patients whose organisms have become resistant to streptomycin during a first course of therapy have generally failed to respond favorably to a second course of streptomycin in the treatment of relapse (5, 9).

In one of the first extensive clinical studies, Muschenheim, et al. (1), reported upon 23 patients with pulmonary tuberculosis, most of whom received 3 grams of streptomycin daily. Eleven patients continued to discharge bacilli throughout the treatment period of seventy-five to one hundred and twenty days. Organisms from 10 of the 11 patients were not inhibited *in vitro* by 500 or more mem. of streptomycin per ml. of medium. Steenken (13), and D'Esopo and

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<sup>4</sup> In this study, the term "streptomycin-resistant tubercle bacilli" refers to organisms whose growth is not inhibited by 10 or more mem. of streptomycin per ml. of Tween-albumin medium. Conversely, the term "streptomycin-sensitive tubercle bacilli" refers to organisms whose growth is inhibited by 10 or less mem. of streptomycin per ml. The selection of 10 mem. of streptomycin per ml. is not entirely arbitrary. Concentrations of this order are maintained in the blood with the dosage used in this study, e.g., 1.0 gram of streptomycin daily in 5 or 6 equally divided doses. More particularly, patients in relapse have responded poorly to retreatment with 1.0 gram of streptomycin daily when organisms were resistant to this concentration of streptomycin *in vitro*. Similar results have been observed in guinea pigs infected with tubercle bacilli resistant to 10 mem. of streptomycin per ml. and treated with comparable dosages.

Steinhaus (5) studied a group of 25 patients treated with 1.8 grams of streptomycin daily for one hundred and twenty days. Eighteen patients continued to discharge bacilli throughout the treatment period. Organisms from 11 of the 18 patients (61 per cent) were not inhibited by 10 or more mem. of streptomycin per ml. of medium. Subsequently, a preliminary report of a coöperative study by the Army, Navy and Veterans Administration (10), which included the data in (5), showed a similar high incidence of strains not inhibited by 10 or more mem. of streptomycin per ml. in patients treated with 1.8 grams of the drug daily for one hundred and twenty days. From the available data, the patients with resistant strains represented 78 per cent of the patients who discharged bacilli throughout the treatment period of one hundred and twenty days.

More recently, dosage regimens of less than 2 grams daily have been undergoing a clinical trial in the treatment of tuberculosis. In addition to variations in therapeutic efficacy and the incidence and severity of toxic manifestations, the incidence and rate of appearance of streptomycin resistant tubercle bacilli in patients treated with these smaller dosages are of considerable interest. It is the purpose of this communication to report upon the *in vitro* sensitivity of tubercle bacilli isolated periodically from a group of 45 patients who were treated with 1.0 gram of streptomycin daily for one hundred and twenty days. The total daily dose was divided into five or six equal parts and administered intramuscularly.

#### MATERIAL AND METHODS

The majority of patients in the study were treated for progressive pulmonary lesions, but those patients treated for extra-thoracic tuberculous lesions had a pulmonary component, and tubercle bacilli were present in the pulmonary secretions of all patients in the study. The extent of the pulmonary lesions, by National Tuberculosis Association standards, was as follows: far advanced, 34; moderately advanced, 11; minimal, 0.

The selection of the 45 cases in the study was made according to the uniform protocol recommended by the Joint Streptomycin Committee, composed of Veterans Administration, Army and Navy Study Units established in May 1946 (10).

Tubercle bacilli were isolated from all patients before streptomycin therapy was begun. During the course of treatment, an attempt was made to isolate tubercle bacilli from the sputum or gastric lavage of each patient every two weeks. In the later stages of the study, weekly cultures were obtained from the fourth through the twelfth weeks of therapy.

Primary isolation of the tubercle bacillus was made on modified Hohn's glycerinated egg media from 72-hour sputum concentrates or fasting gastric contents. Concentrates were prepared by digesting with 3 per cent NaOH plus vigorous shaking and incubation at 37.5 degrees C. for one hour. After centrifugation, the sediment was neutralized with N/1 HCl and seeded on four tubes of media.

Wolinsky and Steenken (11) reported on the usefulness of the Tween<sup>8</sup>-albumin medium described by Dubos and Davis (12) in studying both the development of *in vivo* and *in vitro* resistance of the tubercle bacillus to streptomycin. The formula of the Tween-

<sup>8</sup> Acknowledgment is made to the Atlas Powder Company, Wilmington, Delaware, for supplying this laboratory with the special lot of Tween 80 found suitable for use in Dubos' media.

albumin medium used in this study was essentially that described by the latter investigators. However, the concentration of the bovine albumin fraction was increased from 0.2 per cent to 0.5 per cent; and the concentration of Tween 80 was reduced from 0.05 per cent to 0.02 per cent.

Test tubes 20 mm. in diameter x 150 mm. in length, capped by Aloe-Willet caps of aluminum, were used. These permitted adequate gaseous exchange with minimum danger of contamination.

Each lot of streptomycin used for the preparation of the resistance study media was checked against a streptomycin control standard obtained from the Food and Drug Administration.

Tween-albumin media containing various concentrations of streptomycin were made up in large quantities, and tubed in 5 ml. amounts as needed.

Growth obtained from the original isolation medium was removed with a rigid platinum wire and transferred to the Tween-albumin medium, special attention being paid to triturating the inoculum on one side of the tube in order to produce an even suspension.

TABLE 1  
*Streptomycin sensitivity*

| START OF THERAPY JUNE 5, 1947                        |                          | DAYS GROWTH IN TWEEN-ALBUMIN MEDIUM |    |    |    |
|--|--------------------------|-------------------------------------|----|----|----|
| Case 22  | Conc. Strep.<br>mcm./ml. | 4                                   | 8  | 12 | 14 |
| Gastric culture, date of<br>isolation August 3, 1947 | 0.0                      | 2+                                  | 3+ | 4+ | 4+ |
|  | 0.5                      | 1+                                  | 2+ | 4+ | 4+ |
|  | 1.0                      | +                                   | 1+ | 2+ | 4+ |
|  | 2.5                      | 0                                   | +  | 1+ | 2+ |
|  | 5.0                      | 0                                   | 0  | 0  | 0  |
|  | 10.0                     | 0                                   | 0  | 0  | 0  |
|  | 15.0                     | 0                                   | 0  | 0  | 0  |

Results: Culture resistant to 2.5 mcm. per ml.; sensitive to 5.0 mcm. per ml.

After incubation at 37.5 degrees C. for three days, the cultures in Tween-albumin media were examined for evidence of contamination. Diffuse growth of the inoculated microorganisms was usually noted in three to five days. If, occasionally, the first generation growth was predominantly granular, a second transfer of 0.1 ml. was made to a fresh tube of medium.

Seven to ten days were normally required to obtain heavy diffuse growth of tubercle bacilli. 0.1 ml. of the homogeneous growth was then inoculated into 5 ml. of Tween-albumin medium containing varying concentrations of streptomycin.

The inoculated tubes were incubated at 37.5 degrees C. and readings were made on the fourth, eighth, twelfth and fourteenth days. The tubes were shaken, and the observed turbidity was assigned a value from zero to four plus. The tubes containing no streptomycin usually showed definite growth in four days (one to two plus), while sensitive strains showed no growth when incubated for fourteen days.

The sensitivity of a culture was expressed as the lowest concentration of streptomycin which prevented growth for fourteen days. Occasionally cultures were kept longer when the fourteen-day incubation period did not give a clear endpoint. All reports on streptomycin sensitivity were expressed by two values, the first denoting the highest concentration of streptomycin which permitted growth, the second denoting the lowest concentration which inhibited growth.

In table 1 may be seen a representative record of a typical titration of a gastric or sputum culture. The results recorded represent a culture of gastric contents growing in 2.5 mem. per ml. of streptomycin and inhibited by 5.0 mem. per ml.

The sensitivity of this method for detecting resistant organisms in a mixed bacterial population was described by Wolinsky, Reginster and Steenken (2) in their work on artificial mixtures of streptomycin sensitive and resistant H37 Rv microorganisms. They demonstrated that a concentration of approximately 0.10 per cent of organisms resistant to 1,000 mem. per ml. of streptomycin is necessary before definite growth of a minimal inoculum will be obtained in Tween-albumin media containing 1,000 mem. per ml. of streptomycin when incubated for fourteen days. This study was repeated with organisms isolated from patients, and essentially the same results were obtained: growth of the artificial mixture was obtained when the inoculum contained 0.05 per cent of resistant organisms.

### RESULTS

*Incidence of Streptomycin Resistant Tubercle Bacilli:* From the first 24 of this group of 45 patients, sputum and/or gastric aspirations were cultured approximately every two weeks. From the last 21 patients, weekly cultures were obtained between the fourth and twelfth weeks of therapy as it seemed likely that this was the interval during which streptomycin resistant tubercle bacilli would be demonstrated for the first time with the greatest frequency. The results of *in vitro* sensitivity tests are recorded in table 2. It will be noted that tubercle bacilli from all 45 patients were inhibited by one mem. or less of streptomycin per ml. of medium before therapy was begun. At the completion of the one hundred and twenty days of treatment, tubercle bacilli could be recovered from the sputum or gastric contents of 31 of the 45 patients (69 per cent). At that time, the tubercle bacilli isolated from 26 of the 31 patients required 10 or more mem. of streptomycin per ml. of medium for inhibition of growth. The incidence of streptomycin resistant strains by this method was thus 84 per cent in the patients who continued to have positive cultures throughout the one hundred and twenty days of therapy, and 59 per cent in the total group of patients in the study. Sixty-nine per cent of the resistant strains of tubercle bacilli were capable of growth in 1,000 or more mem. of streptomycin per ml. of medium. The tubercle bacilli from 5 patients (cases 4, 9, 16, 22 and 40) remained sensitive to streptomycin throughout the one hundred and twenty days of therapy, and continued to be sensitive when last tested (average period of eight months after cessation of treatment). Of the 45 patients in the study, there were 14 patients from whom tubercle bacilli could not be recovered at the end of the treatment period. Six of the 14 patients had negative sputum and/or gastric cultures at the end of the fourth week of treatment; and 9, at the end of the sixth week. Sputum and/or gastric cultures of the remaining 5 patients had become negative by the tenth week of therapy.

*Time of Development of Resistant Tubercle Bacilli:* In table 3 is recorded the range of sensitivity of tubercle bacilli from 45 patients in relation to weeks of therapy. In this table it may be seen that the rate of development of resistant tubercle bacilli was greatest during the second month of therapy. While only 3 per cent of positive cultures were titrated as resistant at the end of the fourth

week of therapy, 29 per cent and 53 per cent of positive cultures were resistant at the end of the sixth and eighth weeks of therapy, respectively. From the end

TABLE 2

*Sensitivity to streptomycin of tubercle bacilli isolated periodically from patients under treatment with 1.0 gram of streptomycin per day for four months*

| CASE<br>NUM-<br>BER | BEFORE<br>TREAT-<br>MENT | AFTER 4<br>WEEKS<br>TREAT-<br>MENT* | AFTER 6<br>WEEKS<br>TREATMENT | AFTER 8<br>WEEKS<br>TREATMENT | AFTER 10<br>WEEKS<br>TREATMENT | AFTER 12<br>WEEKS<br>TREATMENT | AFTER 14<br>WEEKS<br>TREATMENT | AFTER 16<br>WEEKS<br>TREATMENT | AFTER 18<br>WEEKS<br>TREATMENT |
|---------------------|--------------------------|-------------------------------------|-------------------------------|-------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| 1                   | 0.0-0.5                  | Neg.                                | Neg.                          | Neg.                          | Neg.                           | Neg.                           | Neg.                           | Neg.                           | Neg.                           |
| 2                   | 0.0-0.5                  | S                                   | S                             | 15-31                         | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     |
| 3                   | 0.0-0.5                  | Neg.                                | Neg.                          | Neg.                          | Neg.                           | Neg.                           | Neg.                           | Neg.                           | Neg.                           |
| 4                   | 0.0-0.5                  | S                                   | S                             | S                             | S                              | S                              | S                              | S                              | 0.5-1.0                        |
| 5                   | 0.0-0.5                  | —                                   | Over 1,000                    | Over 1,000                    | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     |
| 6                   | 0.0-0.5                  | —                                   | 31-62                         | 31-62                         | 31-62                          | 31-62                          | 31-62                          | Over 1,000                     | Over 1,000                     |
| 7                   | 0.0-0.5                  | S                                   | S                             | S                             | Neg.                           | Neg.                           | Neg.                           | Neg.                           | Neg.                           |
| 8                   | 0.0-0.5                  | S                                   | S                             | S                             | S                              | S                              | S                              | 5.0-10.0                       | 5.0-10.0                       |
| 9                   | 0.0-0.5                  | S                                   | S                             | S                             | S                              | S                              | S                              | S                              | 1.0-2.5                        |
| 10                  | 0.0-0.5                  | S                                   | S                             | S                             | —                              | 62-125                         | 31-62                          | 62-125                         | 62-125                         |
| 11                  | 0.0-0.5                  | S                                   | S                             | S                             | S                              | S                              | Neg.                           | Neg.                           | Neg.                           |
| 12                  | 0.0-0.5                  | S                                   | 5.0-10.0                      | 31-62                         | 31-62                          | 31-62                          | 62-125                         | 125-250                        | 125-250                        |
| 13                  | 0.0-0.5                  | S                                   | S                             | S                             | S                              | S                              | S                              | S                              | Over 1,000                     |
| 14                  | 0.0-0.5                  | 5.0-10.0                            | 5.0-10.0                      | 10-15                         | 31-62                          | 31-62                          | 31-62                          | 31-62                          | 31-62                          |
| 15                  | 0.0-0.5                  | Neg.                                | Neg.                          | Neg.                          | Neg.                           | Neg.                           | Neg.                           | Neg.                           | Neg.                           |
| 16                  | 0.0-0.5                  | S                                   | S                             | S                             | S                              | S                              | S                              | S                              | 1.0-2.5                        |
| 17                  | 0.0-0.5                  | S                                   | Neg.                          | Neg.                          | Neg.                           | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     |
| 18                  | 0.0-0.5                  | S                                   | Neg.                          | Neg.                          | Neg.                           | Neg.                           | Neg.                           | Neg.                           | Neg.                           |
| 19                  | 0.0-0.5                  | S                                   | —                             | Over 1,000                    | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     |
| 20                  | 0.0-0.5                  | S                                   | S                             | S                             | 62-125                         | 62-125                         | 62-125                         | 62-125                         | 62-125                         |
| 21                  | 0.0-0.5                  | S                                   | S                             | S                             | S                              | 250-500                        | 250-500                        | 250-500                        | 250-500                        |
| 22                  | 0.0-0.5                  | S                                   | S                             | S                             | S                              | S                              | S                              | S                              | 2.5-5.0                        |
| 23                  | 0.0-0.5                  | S                                   | Neg.                          | Neg.                          | Neg.                           | Neg.                           | Neg.                           | Neg.                           | Neg.                           |
| 24                  | 0.0-0.5                  | S                                   | 10-15                         | 10-15                         | 10-15                          | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     |
| 25                  | 0.0-0.5                  | S                                   | S                             | S                             | S                              | Neg.                           | Neg.                           | Neg.                           | Neg.                           |
| 26                  | 0.0-0.5                  | S                                   | S                             | Neg.                          | Neg.                           | Neg.                           | Neg.                           | Neg.                           | Neg.                           |
| 27                  | 0.0-0.5                  | S                                   | S                             | S                             | Neg.                           | Neg.                           | Neg.                           | Neg.                           | Over 1,000                     |
| 28                  | 0.0-0.5                  | S                                   | S                             | 15-31                         | 15-31                          | 15-31                          | Over 1,000                     | Over 1,000                     | Over 1,000                     |
| 29                  | 0.0-0.5                  | Neg.                                | Neg.                          | Neg.                          | Neg.                           | Neg.                           | Neg.                           | Neg.                           | Neg.                           |
| 30                  | 0.0-0.5                  | S                                   | S                             | Over 1,000                    | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     |
| 31                  | 0.0-0.5                  | S                                   | S                             | S                             | Neg.                           | Neg.                           | Neg.                           | Neg.                           | Neg.                           |
| 32                  | 0.0-0.5                  | Neg.                                | Neg.                          | Neg.                          | Neg.                           | Neg.                           | Neg.                           | Neg.                           | Neg.                           |
| 33                  | 0.0-0.5                  | S                                   | S                             | S                             | 15-31                          | 15-31                          | 15-31                          | Over 1,000                     | Over 1,000                     |
| 34                  | 0.0-0.5                  | S                                   | S                             | Over 1,000                    | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     |
| 35                  | 0.0-0.5                  | S                                   | S                             | Over 1,000                    | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     |
| 36                  | 0.0-0.5                  | S                                   | 15-31                         | Over 1,000                    | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     |
| 37                  | 0.0-0.5                  | S                                   | S                             | 10-15                         | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     |
| 38                  | 0.5-1.0                  | Neg.                                | Neg.                          | Neg.                          | Neg.                           | Neg.                           | Neg.                           | Neg.                           | Neg.                           |
| 39                  | 0.5-1.0                  | S                                   | S                             | Neg.                          | Neg.                           | Neg.                           | Neg.                           | Neg.                           | Neg.                           |
| 40                  | 0.0-0.5                  | S                                   | S                             | S                             | S                              | S                              | S                              | S                              | 1.0-2.5                        |
| 41                  | 0.0-0.5                  | S                                   | S                             | Over 1,000                    | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     |
| 42                  | 0.0-0.5                  | S                                   | Over 1,000                    | Over 1,000                    | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     | Over 1,000                     |
| 43                  | 0.0-0.5                  | S                                   | 5.0-10.0                      | 10-15                         | 10-15                          | 10-15                          | 15-31                          | 15-31                          | 31-62                          |
| 44                  | 0.0-0.5                  | S                                   | 5.0-10.0                      | 15-31                         | 15-31                          | 15-31                          | 15-31                          | 31-62                          | 31-62                          |
| 45                  | 0.5-1.0                  | S                                   | 31-62                         | 31-62                         | 31-62                          | 31-62                          | Over 1,000                     | Over 1,000                     | Over 1,000                     |

S Denotes a sensitive strain which is inhibited by 5.0 mem. per ml. streptomycin or less.

— Denotes failure to obtain a specimen during the specified time interval.

\* All strains prior to this period were inhibited by 1.0 mem. per ml. of streptomycin or less.

of the tenth week of therapy to the end of the eighteenth week, the incidence of resistant cultures increased at an appreciably slower rate. As the percentage of

resistant cultures increased throughout the treatment period, the range in resistance to streptomycin also increased; so that at the end of treatment, tubercle bacilli of 18 of the 26 resistant cultures were capable of growth in 1,000 or more mem. of streptomycin per ml. of medium. The tubercle bacilli from two patients (cases 13 and 27) became resistant for the first time during the last week of therapy. Sputum and gastric cultures from one of these patients (case 27) were negative after ten weeks of treatment, and remained negative until the final day of treatment, when a positive gastric culture was obtained. Organisms from this culture grew readily in over 1,000 mem. per ml. of streptomycin. Resistant tubercle bacilli were subsequently recovered after completion of treatment.

TABLE 3

*Range of sensitivity to streptomycin of tubercle bacilli isolated from patients under treatment with 1.0 gram of streptomycin per day for four months (120 days)*

| MEM. OF<br>STREPTOMY-<br>CIN PER ML.<br>OF MEDIA<br>NECESSARY<br>TO INHIBIT<br>GROWTH | BEFORE<br>TREAT-<br>MENT |                        | AFTER 2<br>WEEKS<br>TREAT-<br>MENT |                        | AFTER 4<br>WEEKS<br>TREAT-<br>MENT |                        | AFTER 6<br>WEEKS<br>TREAT-<br>MENT |                        | AFTER 8<br>WEEKS<br>TREAT-<br>MENT |                        | AFTER 10<br>WEEKS<br>TREAT-<br>MENT |                        | AFTER 12<br>WEEKS<br>TREAT-<br>MENT |                        | AFTER 14<br>WEEKS<br>TREAT-<br>MENT |                        | AFTER 16<br>WEEKS<br>TREAT-<br>MENT |                        | AFTER 18<br>WEEKS<br>TREAT-<br>MENT |                        |
|---|--------------------------|------------------------|------------------------------------|------------------------|------------------------------------|------------------------|------------------------------------|------------------------|------------------------------------|------------------------|-------------------------------------|------------------------|-------------------------------------|------------------------|-------------------------------------|------------------------|-------------------------------------|------------------------|-------------------------------------|------------------------|
|   | Number                   | Per cent of pos. cult. | Number                             | Per cent of pos. cult. | Number                             | Per cent of pos. cult. | Number                             | Per cent of pos. cult. | Number                             | Per cent of pos. cult. | Number                              | Per cent of pos. cult. | Number                              | Per cent of pos. cult. | Number                              | Per cent of pos. cult. | Number                              | Per cent of pos. cult. | Number                              | Per cent of pos. cult. |
| 0.5 or less   | 42                       | 94                     | 42                                 | 94                     | 23                                 | 62                     | 7                                  | 21                     | 5                                  | 14.5                   | 2                                   | 7                      | 2                                   | 6.5                    | 1                                   | 3.5                    | 0                                   | 0                      | 0                                   | 0                      |
| 0.6 to 1.0  | 3                        | 6                      | 2                                  | 4                      | 8                                  | 22                     | 6                                  | 17.5                   | 5                                  | 14.5                   | 3                                   | 10                     | 2                                   | 6.5                    | 1                                   | 3.5                    | 1                                   | 3.5                    | 1                                   | 3                      |
| 2.0 to 5.0  | 0                        | 0                      | 1                                  | 2                      | 5                                  | 13.5                   | 11                                 | 32                     | 6                                  | 17.5                   | 5                                   | 16.5                   | 4                                   | 13                     | 5                                   | 16.5                   | 5                                   | 16.5                   | 4                                   | 13                     |
| 10 to 31  | 0                        | 0                      | 0                                  | 0                      | 1                                  | 2.5                    | 6                                  | 17.5                   | 7                                  | 21.0                   | 5                                   | 16.5                   | 4                                   | 13                     | 3                                   | 10                     | 2                                   | 7                      | 1                                   | 3                      |
| 62 to 125   | 0                        | 0                      | 0                                  | 0                      | 0                                  | 0                      | 2                                  | 6                      | 3                                  | 9                      | 5                                   | 16.5                   | 6                                   | 19                     | 5                                   | 16.5                   | 4                                   | 13                     | 5                                   | 16                     |
| 250 to 500  | 0                        | 0                      | 0                                  | 0                      | 0                                  | 0                      | 0                                  | 0                      | 0                                  | 0                      | 0                                   | 0                      | 1                                   | 3                      | 1                                   | 3.5                    | 2                                   | 7                      | 2                                   | 7                      |
| Over 1,000  | 0                        | 0                      | 0                                  | 0                      | 0                                  | 0                      | 2                                  | 6                      | 8                                  | 23.5                   | 10                                  | 33.5                   | 12                                  | 39                     | 14                                  | 46.5                   | 16                                  | 53                     | 18                                  | 58                     |
| Tot. 1.0 or Less.....   | 45                       | 100                    | 42                                 | 94                     | 31                                 | 84                     | 13                                 | 38                     | 10                                 | 29                     | 5                                   | 16.5                   | 4                                   | 13                     | 2                                   | 7                      | 1                                   | 3.5                    | 1                                   | 3                      |
| Tot. 5.0 or less.....   | 45                       | 100                    | 45                                 | 100                    | 36                                 | 97.5                   | 24                                 | 71                     | 16                                 | 47                     | 10                                  | 33                     | 8                                   | 26                     | 7                                   | 23                     | 6                                   | 20                     | 5                                   | 16                     |
| Tot. 10.0 or more.  | 0                        | 100                    | 0                                  | 0                      | 1                                  | 2.5                    | 10                                 | 29                     | 18                                 | 53                     | 20                                  | 67                     | 23                                  | 74                     | 23                                  | 77                     | 24                                  | 80                     | 26                                  | 84                     |
| Total .....   | 45                       |                        | 45                                 |                        | 37                                 |                        | 34                                 |                        | 34                                 |                        | 30                                  |                        | 31                                  |                        | 30                                  |                        | 30                                  |                        | 31                                  |                        |

The rapid increase in the incidence of streptomycin resistant tubercle bacilli during the fifth to the eighth week of therapy is the most significant of the results presented in this table. It will also be noted (table 3) that in the case of approximately one-third of those patients whose tubercle bacilli became resistant, there was but a two week interval between a culture that was inhibited by 10 or less mem. of streptomycin per ml. of medium, and a subsequent culture that showed growth in over 1,000 mem. of streptomycin per ml. of medium. The cultures from other patients gained this range of resistance to streptomycin at a somewhat slower rate, or remained in an intermediate range, as shown by growth in 31 mem. of streptomycin per ml. of medium, and inhibition of growth in 62 mem. of the drug per ml. of medium. In one patient (case 41) three sputum specimens were inadvertently cultured during a single week of the treatment

period. The tubercle bacilli obtained from a culture inoculated on the fifty-fourth day of treatment were inhibited by less than 2.5 mcm. per ml. of streptomycin, but the organisms obtained two days later, on the fifty-sixth day of treatment, grew in over 15.0 mcm. per ml., but were inhibited by 30.0 mcm. per ml. of the drug. Tubercle bacilli from a culture obtained five days later (sixty-first day of treatment) showed almost a hundred-fold increase in resistance over the previous culture, growing in over 1,000 mcm. per ml. of streptomycin.

*The Persistence of Streptomycin Sensitivity and Resistance:* In Table 4 are recorded preliminary observations upon the persistence of streptomycin resistance or sensitivity after the cessation of streptomycin therapy. It may be seen that in the group of patients from whom such data are available, there has been no

TABLE 4

*Persistence of sensitivity or resistance to streptomycin of strains of tubercle bacilli isolated from patients after treatment*

| CASE NUMBER | MCM./ML. STREPTOMYCIN NECESSARY TO INHIBIT ISOL. AFTER COMPLETION OF 120 DAYS TREATMENT | MCM./ML. STREPTOMYCIN NECESSARY TO INHIBIT |                 |
|-------------|---|--|-----------------|
|             |   | Months after treat.                        | Mcm./ml. strep. |
| 2           | Over 1,000  | 7  | Over 1,000      |
| 4           | 0.5-1.0   | 4  | 1.0-2.5         |
| 8           | 5.0-10.0  | 3  | 5.0-10.0        |
| 9           | 1.0-2.5   | 6  | 1.0-2.5         |
| 10          | 125-250   | 4  | 125-250         |
| 16          | 1.0-2.5   | 5  | 1.0-2.5         |
| 17          | Over 1,000  | 7  | Over 1,000      |
| 19          | Over 1,000  | 1*   | Over 1,000      |
| 21          | 250-500   | 6  | 250-500         |
| 22          | 2.5-5.0   | 4  | 2.5-5.0         |
| 24          | Over 1,000  | 2*   | Over 1,000      |
| 28          | Over 1,000  | 4  | Over 1,000      |
| 30          | Over 1,000  | 4  | Over 1,000      |
| 33          | Over 1,000  | 5  | Over 1,000      |
| 36          | Over 1,000  | 1*   | Over 1,000      |

\* Represents cultures obtained from material at autopsy.

change in the sensitivity of those organisms obtained at the end of the one hundred and twenty days of therapy and those most recently isolated at an average interval of five months after completion of therapy. Cases 19, 24 and 36 represent cultures obtained from autopsy specimens. Autopsy material obtained from case 24 included 7 specimens from separate sections of right and left lungs, and one specimen from empyema fluid. All these cultures grew in over 1,000 mcm. per ml. of streptomycin.

#### COMMENT

The significance of the data herein reported depends entirely upon the validity of the test used to demonstrate streptomycin resistant tubercle bacilli. As previously mentioned, an extremely small proportion of resistant tubercle bacilli

is sufficient to permit growth of artificial mixtures in the presence of streptomycin. If a correspondingly small proportion of resistant tubercle bacilli were present in a lesion under streptomycin therapy, it could not be assumed that streptomycin would be totally ineffective. In the final analysis, then, the clinical significance of sensitivity tests by this method depends upon their correlation with the clinical course of individual patients under therapy. Preliminary studies do, indeed, suggest that such correlations exist in a significant proportion of patients (5, 9).

The present data suggest that the incidence of streptomycin resistant tubercle bacilli in patients treated with one gram of streptomycin daily does not differ significantly from that previously noted in the patients treated with larger dosages, namely, two and three grams daily for one hundred and twenty days. The similarity is further emphasized by the fact that the greatest rate of appearance of resistant tubercle bacilli occurred during the second month of therapy in patients treated with 1.0 and 1.8 grams of streptomycin daily.

#### SUMMARY

1. Forty-five patients with pulmonary tuberculosis were treated with 1.0 gram of streptomycin daily, divided in five or six equal doses, for a period of one hundred and twenty days.

2. Tubercle bacilli isolated prior to therapy from all 45 patients were sensitive to 1.0 mcm. or less of streptomycin per ml. of medium.

3. After one hundred and twenty days of streptomycin treatment, tubercle bacilli were recovered from the sputum or gastric contents of 31 of the 45 patients (69 per cent).

4. Tubercle bacilli resistant to 10 or more mcm. of streptomycin per ml. were recovered from 26 of the 31 patients (84 per cent). Eighteen strains were capable of growth in over 1,000 mcm. of streptomycin per ml. of media.

5. The rate of development of streptomycin resistant tubercle bacilli was greatest during the second month of therapy.

#### SUMARIO

##### *Bacilos Tuberculosos Estreptomycinorresistentes. Incidencia en los Enfermos Tratados con Estreptomicina*

1. Cuarenta y cinco tuberculosos pulmonares fueron tratados, por espacio de 120 días, con 1.0 gramo diario de estreptomicina, fraccionado en cinco o seis dosis iguales.

2. Los bacilos tuberculosos aislados de los 45 enfermos antes del tratamiento eran sensibles a 1.0 mcm. o menos de estreptomicina por cc. de medio.

3. Al cabo de 120 días de estreptomycinoterapia, se aislaron bacilos tuberculosos del esputo o contenido gástrico de 31 (69 por ciento) de los 45 enfermos.

4. De 26 (84 por ciento) de los 31 enfermos se obtuvieron bacilos tuberculosos resistentes a 10 mcm. o más de estreptomicina por cc. Dieciocho cepas mostraron capacidad para el desarrollo en más de 1000 mcm. de estreptomicina por cc. de medio.



5. La aparición de bacilos tuberculosos estreptomycinorresistentes alcanzó su máximo durante el segundo mes de la terapéutica.

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# STREPTOMYCIN IN EXPERIMENTAL TUBERCULOSIS<sup>1,2,3,4,5</sup>

## II. Response in Guinea Pigs Infected with Strains of Varying Degrees of Streptomycin Resistance

WILLIAM STEENKEN, JR. AND EMANUEL WOLINSKY

Many workers (1, 2, 3, 4, 5) have demonstrated that guinea pigs and mice infected with virulent, human type tubercle bacilli which are sensitive to the action of streptomycin *in vitro* respond remarkably well to treatment with adequate doses of this drug. In contrast, Youmans (6) has shown that mice infected with tubercle bacilli resistant to the drug do not respond to treatment with streptomycin. Feldman et al. (7) have confirmed this finding in guinea pigs.

It is the purpose of this report to present the results of streptomycin therapy in guinea pigs infected with: (1) highly streptomycin-resistant human type tubercle bacilli introduced subcutaneously and by inhalation; (2) tubercle bacilli of varying degrees of drug-resistance; (3) artificial mixtures of drug-sensitive and drug-resistant H37 Rv tubercle bacilli.

### EXPERIMENTAL OBSERVATIONS

#### Highly Resistant Tubercle Bacilli

*Materials and Methods.* The cultures used were as follows:

1. The H37 Rv strain of microorganisms, sensitive to 0.4 mem. of streptomycin per cc. of medium.<sup>1</sup>

2. The H37 Rv strain made resistant to at least 1,000 mem. of streptomycin per cc. of medium. This culture was made resistant by growing the organisms in gradually increased concentrations of streptomycin in Tween-albumin liquid medium of Dubos (9).

3. Streetman (September 13, 1946). This culture was obtained from the sputum of a patient treated with streptomycin for pulmonary tuberculosis at the Veterans Hospital, Sunnount, New York. This patient's tubercle bacilli were sensitive to 0.5 mem. of streptomycin per cc. before treatment was started. On September 13, after one month of treatment, the bacilli proved to be resistant to 1,000 mem. per cc., growth appearing in the 1,000 mem. tube on the fourteenth day.

<sup>1</sup> From the Trudeau Laboratory of The Trudeau Foundation for The Clinical and Experimental Study of Pulmonary Disease, Trudeau, New York.

<sup>2</sup> This study is part of the Streptomycin Tuberculosis Research Project of the American Trudeau Society, Medical Section, National Tuberculosis Association. The drug was generously donated to the Society by Abbott Laboratories, Eli Lilly and Company, Merck and Company, Inc., Charles Pfizer and Company, Inc., E. R. Squibb and Sons, and The Upjohn Company.

<sup>3</sup> This study was aided by grants from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service.

<sup>4</sup> Parts of this paper were presented at the Third and the Fourth Streptomycin Conferences of the Veterans Administration, St. Louis, May and October, 1947.

<sup>5</sup> Parts of this paper were presented at the Forty-eighth General Meeting of the Society of American Bacteriologists, Minneapolis, May 1948.

<sup>6</sup> Streptomycin sensitivities of tubercle bacilli referred to in this paper were determined by the method previously described (8), using fourteen-day observations in Tween-albumin liquid medium at pH 7.0.

The cultures were carried for several generations in Tween-albumin liquid medium, and the animals were infected with a diffuse, five- to eight-day growth in this medium.

*Subcutaneous Infection:* The culture was adjusted to a turbidity reading of 25 in the Klett-Summerson photoelectric colorimeter, using the green filter, by diluting with Tween-albumin medium. Each pig was inoculated with 0.2 cc. of this culture, or approximately 0.02 mg. dry weight, subcutaneously in the right inguinal region.

The animals were infected, grouped and treated as follows:

- Group 1. Infected with H37 Rv sensitive to streptomycin;  
46 pigs: 27 untreated controls and 19 streptomycin-treated;
- Group 2. Infected with H37 Rv resistant to 1,000 mem. of streptomycin per cc.;  
48 pigs: 28 untreated controls and 20 streptomycin-treated;
- Group 3. Infected with Streetman culture, resistant to 1,000 mem. of streptomycin per cc.;  
46 pigs: 26 untreated controls and 20 streptomycin-treated.

The treated animals were started on streptomycin twenty-eight days after infection. They were given 18,000 mem. intramuscularly daily; 4,000 mem. at 7:30 A.M., 12:30 and 5:30 P.M., and 6,000 mem. at 10:30 P.M. One hundred days after infection, or seventy-two days after treatment was started, all survivors were killed and autopsied.

*Inhalation Infection:* The Tween-albumin culture was diluted five times with normal saline and filtered through double thickness Whatman No. 5 filter paper to give a diffuse suspension. This suspension was diluted so that when a standard loopful was smeared on a micro-slide over the area of 20 x 20 mm., each oil immersion field would contain about five tubercle bacilli. Each pig was subjected to five puffs of this suspension from a De Vilbiss atomizer, the animal's head being enclosed in a small chamber.

Forty pigs were subjected to inhalation of the H37 Rv organisms resistant to 1,000 mem. of streptomycin per cc. Of these, 4 failed to develop positive skin tests with 5 per cent Old Tuberculin, and were discarded. Five animals were killed for sampling the amount of disease before treatment was started. The remaining 31 pigs were divided into two groups, 14 untreated controls, and 17 treated. The treated animals were started on streptomycin fifty days after infection. They were given 20,000 mem. per day intramuscularly, in doses of 10,000 mem. every twelve hours. The survivors were killed and autopsied one hundred days after infection, fifty days after treatment was started.

### Results

A number of animals from each group were sacrificed just before treatment was started to observe the type and degree of tuberculosis. In each case, widespread tuberculosis was found throughout the animal body, which indicated that a generalized, progressive tuberculosis was to be treated.

The survival curves of the guinea pigs infected with the different cultures are presented in figures 1 and 2. It is obvious from the curves that the animals infected with the H37 Rv sensitive strain responded very well to treatment with streptomycin, none of the treated animals dying, whereas 77 per cent of the control animals succumbed from the fortieth to the one hundredth day. In contrast, in the groups infected with streptomycin-resistant tubercle bacilli, the streptomycin-treated animals fared no better than the untreated controls. In fact, the treated animals began to die sooner and at a more rapid rate than the controls. This held true both in the subcutaneously infected group, and the group infected by inhalation.

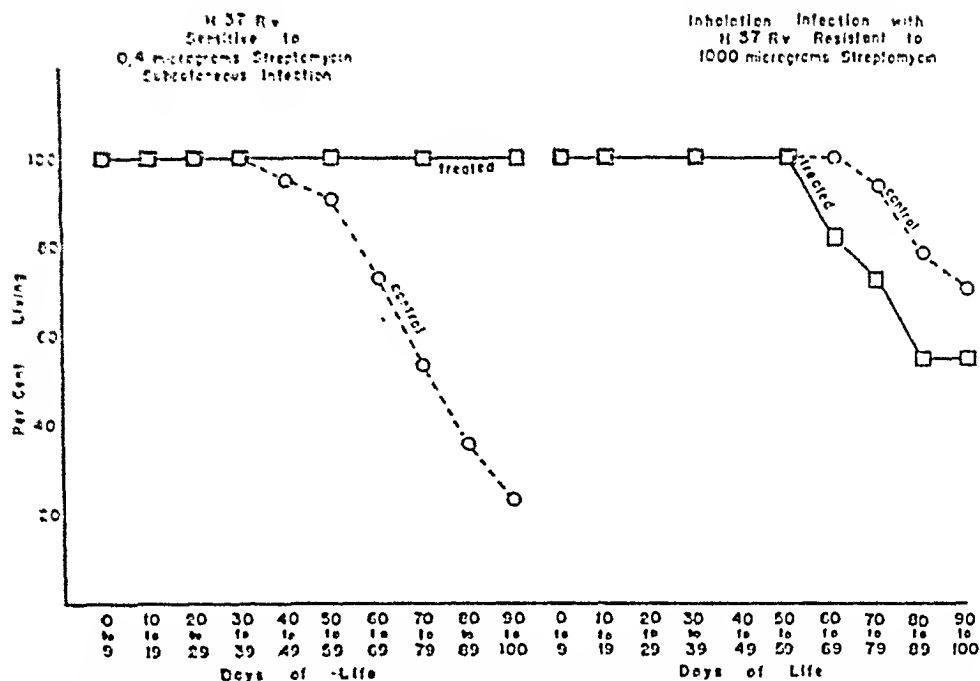


FIG. 1. Survival curves of guinea pigs infected with streptomycin-sensitive H 37 Rv culture subcutaneously, and streptomycin-resistant H 37 Rv culture by inhalation.

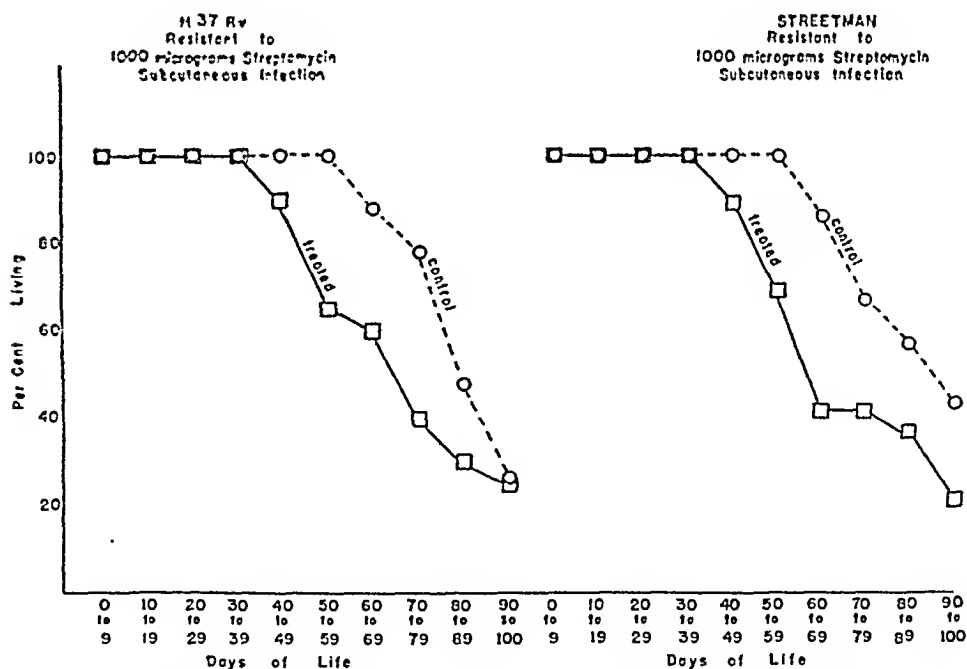


FIG. 2. Survival curves of guinea pigs infected with streptomycin-resistant H 37 Rv and Streetsman cultures.

In table 1 are recorded the mortality, the average number of days of life of those pigs that died of tuberculosis, and the average degree of tuberculous disease at death or when killed at the end of the experiment. It is obvious that the animals infected with streptomycin-resistant organisms did not receive benefit from streptomycin treatment. The mortality was, in general, greater in the treated groups than in the controls, and the average days of life tended to be less in the treated groups. There was no significant difference in the average degree of tuberculosis between the treated and the control groups.

### Tubercle Bacilli of Varying Degrees of Drug Resistance

Early in the study of the frequency and rapidity of the emergence of streptomycin-resistant tubercle bacilli in patients undergoing drug therapy (10), the

TABLE 1

*Effect of streptomycin in guinea pigs infected with drug-resistant tubercle bacilli, as contrasted to those infected with a drug-sensitive strain*

| INFECTED WITH                     | TREATMENT         | 100-DAY<br>MORTALITY | AVERAGE DAYS<br>OF LIFE OF<br>THOSE THAT DIED | AVERAGE<br>AMOUNT OF TU-<br>BERCULOSIS AT<br>DEATH OR SACRI-<br>FICE <sup>1</sup> |
|-----------------------------------|-------------------|----------------------|---|---|
|                                   |                   | <i>per cent</i>      |   |   |
| H 37 Rv, sensitive,<br>subcut.    | Controls (27)     | 77                   | 93  | 14.3  |
|                                   | Streptomycin (19) | 0                    | —   | —   |
| H 37 Rv, resistant,<br>subcut.    | Controls (28)     | 74                   | 84  | 15.2  |
|                                   | Streptomycin (20) | 75                   | 66  | 13.8  |
| Streetman, resistant,<br>subcut.  | Controls (26)     | 57                   | 61  | 14.7  |
|                                   | Streptomycin (20) | 80                   | 60  | 12.5  |
| H 37 Rv, resistant,<br>inhalation | Controls (14)     | 29                   | 82  | 11.2  |
|                                   | Streptomycin (17) | 65                   | 76  | 12.7  |

<sup>1</sup> Based on maximum of 16 for each animal; maximum of 4 each for lungs, liver, spleen, and lymph nodes, as observed grossly at autopsy.

question arose as to what degree of resistance a culture must exhibit before being classified as a "resistant strain." The highly resistant strains, which grow in the presence of 100 to 1,000 mem. of streptomycin per cc. of medium, and the very sensitive strains, which are inhibited by 2.0 or less mem. per cc., are easily classified. It is the group of cultures of intermediate sensitivity, requiring 2.5 to 50 mem. per cc. for inhibition in liquid medium, which prove difficult to classify.

In an attempt to clarify this problem, groups of 10 guinea pigs were infected with 21 cultures of intermediate sensitivity, varying from 0.5 to 250 mem. per cc. of medium, which had been isolated from patients under streptomycin therapy. This experiment also served as a comparison of the *in vitro* sensitivity, as obtained by the particular method in use at this laboratory, with the *in vivo* sensitivity in guinea pigs.

Five animals in each group were started on streptomycin therapy fourteen to thirty days after subcutaneous infection with 0.02 mg. (dry weight) of micro-organisms, each pig receiving 10,000 mcm. of the drug intramuscularly every twelve hours. All surviving animals were sacrificed ninety days after infection. At autopsy, cultures were made from the tissues of several treated and control animals in each group, and the tubercle bacilli recovered were tested for streptomycin sensitivity.

### Results

In table 2, the treated and control animals in each group are compared as to the gross degree of tuberculous disease and the streptomycin sensitivity of the recovered strains. The results, in general, indicate that those strains which are resistant *in vitro* to 15 or more mcm. per cc. of medium are also resistant *in vivo*, i.e., guinea pigs infected with such strains are not benefited by streptomycin treatment. Also, those strains which are sensitive to 2.5 or less mcm. per cc. are usually sensitive *in vivo*. The results, however, reveal many inconsistencies for strains of borderline resistance. For example, strain E. L. with an *in vitro* sensitivity of 10 mcm. per cc., responded well to therapy, whereas others, exhibiting approximately the same *in vitro* sensitivity, responded poorly. Strain W. B. isolated twenty-three days after therapy was begun, and completely sensitive *in vitro*, responded well in the guinea pigs, but when isolated on the eighty-fourth day of treatment, although still relatively sensitive *in vitro*, proved to be almost completely resistant in the animals. Strain A. Z. isolated on the forty-second day of therapy, and sensitive to between 5 and 10 mcm. per cc., gave as good a response in the animals as some completely sensitive cultures.

It might be suggested that the lack of response to therapy in some groups was due to the survival of the resistant forms at the expense of the sensitive forms in the original culture, thereby producing a population of bacilli of greatly increased resistance. Examination of the data in the table, reveals, however, that the strains recovered from both the treated and the control animals exhibited essentially the same streptomycin sensitivities as the original infecting cultures. Strain A. Z. (isolated on the forty-second day) recovered from the control animals was sensitive to 2.5 mcm. per cc.; when cultured from the treated animals, it was sensitive to between 10 and 30 mcm. per cc. This was the most significant increase in resistance, and yet, the guinea pigs infected with this strain responded very well to drug therapy.

### Artificial Mixtures of Sensitive and Resistant Bacilli

Starting with two H37 Rv cultures, one completely sensitive to streptomycin, and the other resistant to at least 1,000 mcm. per cc. of medium, artificial mixtures were made in Tween-albumin liquid medium to contain various proportions of sensitive and resistant forms. Five groups of guinea pigs, each group numbering 15 animals, were infected as follows:

- Group 1. 100 per cent streptomycin-sensitive bacilli;
- Group 2. 100 per cent streptomycin-resistant bacilli;

TABLE 2

*Streptomycin treatment in guinea pigs infected with 21 cultures of tubercle bacilli exhibiting intermediate drug resistance in vitro*

| PATIENT | DAYS OF TREATMENT | IN VITRO STREPTOMYCIN SENSITIVITY <sup>1</sup> | RESULTS OF TREATMENT OF GUINEA PIGS      |         |                          | SENSITIVITY OF RECOVERED TUBERCLE BACILLI |                           |     |    |     |                   |              |                 |    |     |
|---------|-------------------|--|--|---------|--------------------------|---|---------------------------|-----|----|-----|-------------------|--------------|-----------------|----|-----|
|         |                   |  | Ave. degree of Tuberculosis <sup>2</sup> |         | Response of treated pigs | Control                                   |                           |     |    |     | Treated           |              |                 |    |     |
|         |                   |  | Control                                  | Treated |                          | Liquid <sup>3</sup>                       | Solid Medium <sup>3</sup> |     |    |     | Liquid            | Solid Medium |                 |    |     |
|         |                   |  |  |         |                          |   | 0                         | 3.5 | 15 | 200 |                   | 0            | 3.5             | 15 | 200 |
| A. Z.   | 21                | 0.5  | 14.6                                     | 1.3     | Excellent                |   |                           |     |    |     | 0.5               | 1            | 0               | 0  | 0   |
|         | 28                | 2.5-5 <sup>5</sup>                             | 14.1                                     | 2.9     | Good                     | 1-2.5 <sup>5</sup>                        | 1+                        | 0   | 0  | 0   | 2.5-10            | 3            | 0               | 0  | 0   |
|         | 42                | 5-10   | 15.0                                     | 3.8     | Good                     | 2.5                                       | 3+                        | 0   | 0  | 0   | 10-30             | 25           | 25              | 15 | 0   |
| E. C.   | 7                 | 0.5  | 13.1                                     | 1.0     | Excellent                | 1.0                                       | 3+                        | 0   | 0  | 0   | Cultures negative |              |                 |    |     |
|         | 22                | 2.5-5  | 15.0                                     | 10.8    | Poor                     | 5.0                                       | 15                        | 2   | 0  | 0   | 10                | 3            | 1+              | 0  | 0   |
|         | 22                | 2.5-5  | 12.6                                     | 11.2    | Poor                     | 5.0                                       | 5                         | 3   | 0  | 0   | 5-10              | 16           | 0               | 0  | 0   |
| W. B.   | 23                | 0.5  | 14.0                                     | 2.8     | Good                     | 1.0                                       | 6                         | 0   | 0  | 0   | Cultures negative |              |                 |    |     |
|         | 84                | 2.5-5  | 14.1                                     | 13.0    | None                     | 2.5-10                                    | 4+                        | 1+  | 0  | 0   | 5.0               | 12           | 1               | 0  | 0   |
| R. H.   | 48                | 0.5  | 14.0                                     | 2.3     | Excellent                | 1.0                                       | 3+                        | 0   | 0  | 0   | 0.5               | 2            | 0               | 0  | 0   |
| R. G.   | 32                | 1-2.5  | 11.0                                     | 6.3     | Fair                     |   |                           |     |    |     | 2.5               | 3            | ct <sup>4</sup> | 0  | 0   |
| A. F.   | 97                | 1-2.5  | 14.5                                     | 10.0    | Poor                     | 2.5                                       | 1+                        | 0   | 0  | 0   | 2.5               | 5            | 0               | 0  | 0   |
| D. F.   | 120               | 2.5  | 14.5                                     | 6.2     | Fair                     | 1-2.5                                     | 2+                        | 0   | 0  | 0   | 2.5               | 3            | ct              | 0  | 0   |
| M. K.   | 31                | 2.5  | 13.6                                     | 1.9     | Excellent                | 0.5-1                                     | 1+                        | 0   | 0  | 0   | Cultures negative |              |                 |    |     |
| T. C.   | 42                | 2.5-5  | 15.5                                     | 10.7    | Poor                     | 1.0                                       | 1                         | 0   | 0  | 0   | 10                | 25           | 7               | 0  | 0   |
| G. D.   | 37                | 5.0  | 14.5                                     | 9.8     | Poor                     | 2.5-5                                     | 3+                        | 1+  | 0  | 0   | 5.0               | 2+           | 1+              | 0  | 0   |
| E. L.   | 47                | 10   | 12.6                                     | 1.5     | Excellent                | 0.5-1                                     | 30                        | 0   | 0  | 0   | Cultures negative |              |                 |    |     |
| M. P.   | 117               | 10-15  | 14.5                                     | 10.5    | Poor                     | 10  | ct                        | 1+  | 0  | 0   | 10                | 15           | 1               | 0  | 0   |
| E. B.   | 45                | 15-30  | 14.5                                     | 11.6    | Poor                     |   |                           |     |    |     | 60-125            | 1+           | 1+              | 30 | 0   |
| N. M.   | 68                | 30-60  | 13.6                                     | 13      | None                     | 30-60                                     | 3+                        | 2+  | 10 | 0   | 60-125            | 3+           | 2+              | 1+ | 0   |
| L. L.   | 103               | 125  | 15.4                                     | 12.5    | Poor                     | 125-250                                   | 2+                        | 2+  | 30 | 0   | 125               | 2+           | 1+              | 10 | 0   |
| J. T.   | 120               | 250  | 12.4                                     | 13.2    | None                     | 500-1000                                  | 2+                        | 2+  | 2+ | 1   | 1000              | 3+           | 2+              | 2+ | 0   |

<sup>1</sup> Lowest concentration of streptomycin inhibiting growth for 14 days in Tween-albumin medium. Concentrations used were: 0 (control), 0.5, 1.0, 2.5, 5.0, 10, 15, 30, 60, 125, 250, 500, and 1,000 mcm. per cc.

<sup>2</sup> Based on a maximum of 16 for each animal (4 each for the lungs, liver, spleen and lymph nodes).

<sup>3</sup> Streptomycin was incorporated into the modified Committec Medium (11) in concentrations of 10, 50, and 500 mcm. per cc. After sterilization and inspissation of the solid medium, the actual concentrations of available streptomycin by chemical analysis were 3.5, 15 and 200 mcm. per cc. The animal tissues, after digestion and concentration, were planted on a series of these tubes containing streptomycin, as well as two tubes of the plain medium. Growth is expressed in terms of one to four plus. If fewer than 50 colonies appeared, the actual number of colonies is recorded in the table. An average value for the positive cultures in each group is given.

<sup>4</sup> Culture contaminated.

<sup>5</sup> Where two values appear, they indicate the range of sensitivities for all the positive cultures obtained from the group of animals.

<sup>6</sup> When two values appear, they indicate the range of results on repeated tests of the same culture.

- Group 3. 10 per cent resistant, 90 per cent sensitive bacilli;  
 Group 4. 1 per cent resistant, 99 per cent sensitive bacilli;  
 Group 5. 0.1 per cent resistant, 99.9 per cent sensitive bacilli.

Each animal was infected with 0.02 mg. (dry weight), or approximately 6,000,000 microorganisms.

Five guinea pigs in each group were left untreated, 5 started on streptomycin therapy immediately, and 5 started thirty-eight days after infection. The dosage used was 10,000 mem. every twelve hours, injected intramuscularly. All survivors were sacrificed one hundred days after infection.

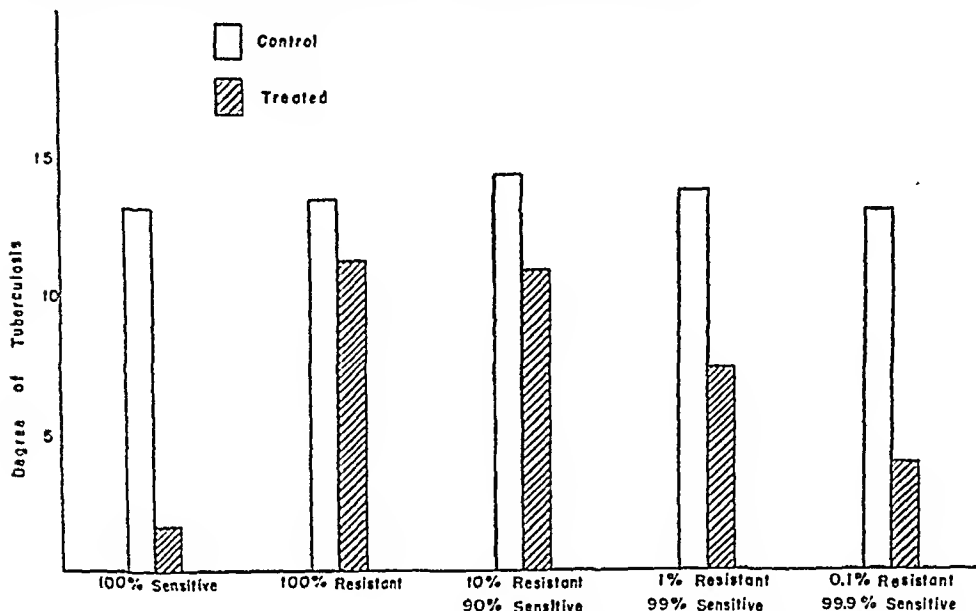


FIG. 3. Comparison of amount of tuberculosis in guinea pigs infected with artificial mixtures of streptomycin-sensitive and streptomycin-resistant tubercle bacilli.

### Results

The results of therapy are shown in figure 3. The average degree of tuberculosis, as seen grossly at autopsy, is indicated by the height of the bar. As there was no significant difference between the animals which received immediate and delayed treatment, they are grouped together under "treated." It is evident that, as the proportion of resistant organisms decreases below 10 per cent, the response to therapy improves. However, even with only 0.1 per cent resistant organisms, representing an inoculum of approximately 6,000 streptomycin-resistant bacilli and 5,994,000 streptomycin-sensitive bacilli, the animals exhibited a significantly greater amount of disease than those infected with the 100 per cent sensitive culture.

### DISCUSSION

The question of whether *in vitro* resistance of tubercle bacilli to streptomycin is equivalent to *in vivo* resistance is an extremely important one. Patients



treated with streptomycin for tuberculosis often yield tubercle bacilli which prove to be resistant to the action of the drug *in vitro*. Should streptomycin be withheld from these patients, or is it possible that they would respond favorably to further treatment despite the *in vitro* resistance of their organisms? Only further correlation between the clinical course of the patient and sensitivity tests will provide the answer. From the experiments reported here, it is evident that guinea pigs infected with two highly streptomycin-resistant human types of tubercle bacilli were not benefited by therapy. In fact, under the particular conditions of these experiments, the animals seemed to be made worse by streptomycin treatment. During the first few weeks of therapy, the treated pigs looked sicker than the controls, and they began to succumb to their disease sooner.

It would appear from the results of the *in vivo* sensitivity tests that an exact definition of a drug-resistant culture cannot be given until further work is done. Evidently, there is no sharp line of demarcation, but a gradual change from drug-sensitive to drug-resistant strains. The *in vitro* test, as it stands today, is not adequate, by itself, to distinguish absolutely between drug-sensitive and drug-resistant strains of tubercle bacilli in the range of intermediate resistance from 2.5 to 30 mc. of streptomycin per cc. of medium.

There are other debatable points raised by these results. Why should not tubercle bacilli which have already acquired a definite degree of streptomycin resistance become increasingly more resistant in the body of a guinea pig undergoing streptomycin therapy? Even the animals that showed no response to treatment, and died of their tuberculosis, yielded organisms of approximately the same resistance as the original culture used for infection. This is in contrast to patients taking streptomycin, whose tubercle bacilli, once they start to become resistant, usually continue to increase in resistance.

Is there some substance in the guinea pig body which possesses the ability to hold back the process of development of drug resistance, or to prevent the mutation of resistant forms to more highly resistant types? This theory might explain the relative difficulty of producing drug-resistant strains of tubercle bacilli in the guinea pig as compared with the ease of producing resistant strains in patients.

It is important to emphasize the results obtained in the treatment of animals infected with the two highly resistant strains. There is no doubt that the treated animals began to succumb sooner than the controls. This fact was observed in three separate experiments, with two different cultures, and with subcutaneous and inhalation infection. The explanation does not lie in an increased virulence of the organisms, nor in the development of streptomycin dependence by the organisms, as it was not possible to demonstrate that either phenomenon had occurred. It is possible that there was an alteration in the host, which became apparent under the conditions of this experiment, *i.e.*, intensive treatment of advanced disease produced by highly drug-resistant bacilli. Further studies are being pursued to evaluate this observation.

## SUMMARY

1. Guinea pigs infected with two highly streptomycin-resistant strains of human tubercle bacilli were not benefited by streptomycin therapy.

2. Under the specific conditions of the reported experiments, the streptomycin-treated guinea pigs infected with these two cultures began to succumb sooner than the untreated animals.

3. Comparisons between *in vitro* streptomycin sensitivity of cultures of tubercle bacilli isolated from patients, with *in vivo* streptomycin sensitivity in guinea pigs, reveals good agreement for cultures sensitive to 2.5 or less mem. per cc., and for those resistant to 15 or more.

4. Some cultures of borderline resistance (sensitive to 5 to 15 mem. per cc.) responded well *in vivo*, others responded poorly.

5. Strains of tubercle bacilli recovered from the streptomycin-treated and from the control animals infected with these cultures of intermediate resistance exhibited essentially the same drug sensitivities as the original infecting cultures.

6. The results of streptomycin therapy in five groups of guinea pigs infected with artificial mixtures containing various proportions of sensitive and resistant H37 Rv microorganisms, indicate that the response to treatment improves as the percentage of resistant organisms decreases below 10 per cent.

## SUMARIO

*La Estreptomicina en la Tuberculosis Experimental: II. Respuesta en los Cobayos Infectados con Cepas Dotadas de Varios Grados de Resistencia a la Estreptomicina*

1. Los cobayos infectados con dos cepas altamente estreptomicinorresistentes de bacilos tuberculosos humanos no se beneficiaron con la estreptomicinoterapia.

2. En las condiciones específicas de los experimentos descritos, los cobayos infectados con dichos dos cultivos y tratados con estreptomicina comenzaron a sucumbir antes que los no tratados.

3. Las comparaciones entre la estreptomicinosensibilidad *in vitro* de los cultivos de bacilos tuberculosos aislados de enfermos y la estreptomicinosensibilidad *in vivo* en los cobayos revelan buen acuerdo para los cultivos sensibles a 2.5 mem. o menos por cc. y para los sensibles a 15 ó más.

4. Algunos cultivos dotados de resistencia fronteriza (sensibles a 5-15 mem. por cc.) respondieron bien, y otros mal, *in vivo*.

5. Las cepas tuberculosas obtenidas de los animales tratados con estreptomicina y de los testigos infectados con los cultivos dotados de resistencia intermedia manifestaron esencialmente la misma sensibilidad a la droga que los primitivos cultivos infectantes.

6. El resultado de la estreptomicinoterapia en cinco grupos de cobayos infectados con mezclas artificiales que contenían varias proporciones de microbios H37 Rv. sensibles y resistentes, indica que la respuesta terapéutica mejora a medida que el porcentaje de gérmenes resistentes baja a menos de 10 por ciento.

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# A STUDY OF CERTAIN PROBLEMS IN THE USE OF STANDARD TUBERCULIN. FRACTIONATION OF PPD, STANDARDIZATION OF TUBERCULINS, AND THE QUESTION OF SENSITIZATION<sup>1, 2</sup>

FLORENCE B. SEIBERT AND EMMA DUFOUR

## INTRODUCTION

Ten years ago a large lot of a purified tuberculin known as Purified Protein Derivative, PPD-S, was prepared (1) which has served as a standard since that time. This lot has been the source of practically all the PPD tuberculin used in this country in recent years. Five years before that, a less pure but potent product was made (2), which, with slight modifications, has been used extensively by some investigators (3, 4, 5).

While the PPD-S marked a decided advance in the direction of purity, it is evident from physicochemical studies that further purification is possible. The following data will help answer some questions that have arisen in the use of this tuberculin. They indicate clearly the possibilities of further purification, which may lead to the production of a more specific product.

## DUPPLICATION OF PPD PREPARATIONS

After preparation of the large quantity of purified tuberculin for use as standard (1), it was important to know whether such a preparation could be duplicated in purity as well as in potency, especially since it has been found difficult to duplicate in potency preparations made by the old trichloroacetic acid precipitation method (5). The reason for this is that there exist in any raw tuberculin a number of different proteins with different degrees of potency. Moreover, in the trichloroacetic preparations there are also present considerable amounts of other impurities, such as nucleic acid and polysaccharide, as will be shown later. All of these constituents may vary with different environmental conditions and also with different strains of tubercle bacilli.

If conditions are kept constant, however, or only minor changes are introduced, it appears to be possible to obtain products of equal potency by means of the ammonium sulfate precipitation at pH 7.0, as used in preparing the PPD-S. For example, one hundred culture bottles of Long's medium were planted with the human strain, DT, and after eight weeks harvested and prepared in exactly the same way as the PPD-S (1), except for the use of phenol instead of tolnol. The product was designated PPD-S1.

The electrophoretic diagrams of PPD-S1 and the PPD-S are shown in figure 1. The chemical analyses for impurities are shown in table 1, and also the relative potencies. The results showed practically equal purity and very little difference

<sup>1</sup> From the Henry Phipps Institute of the University of Pennsylvania, Philadelphia, Pennsylvania.

<sup>2</sup> Aided by grants from the Committee on Medical Research of the National Tuberculosis Association.

in potency in the two preparations when tested in human beings of different sensitivities. It was, therefore, possible to duplicate the product very closely

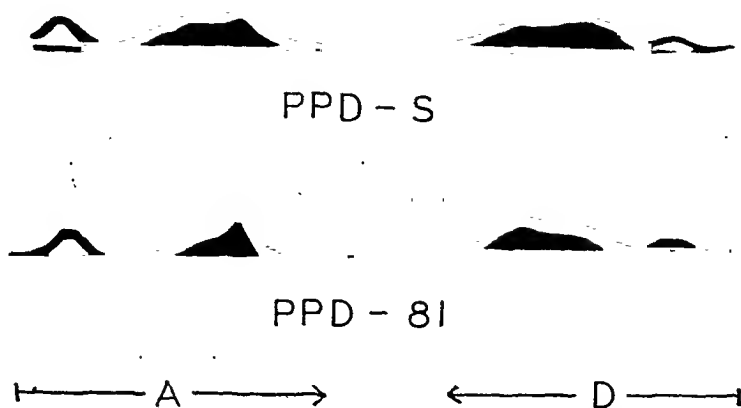


FIG. 1. Ammonium sulphate precipitate at pH 7.0

TABLE 1  
*Relative potencies of purest PPD preparations*

| PREPARATION                | NU-<br>CLEIC<br>ACID | POLY-<br>SAC-<br>CHA-<br>RIDE | SKIN TEST WITH 0.00002 MG. |                              |                                   | SKIN TEST WITH 0.005 MG. |                              |                                   |
|----------------------------|----------------------|-------------------------------|----------------------------|------------------------------|-----------------------------------|--------------------------|------------------------------|-----------------------------------|
|                            |                      |                               | Num-<br>ber<br>tested      | Num-<br>ber<br>posi-<br>tive | Dimensions of average<br>reaction | Num-<br>ber<br>tested    | Num-<br>ber<br>posi-<br>tive | Dimensions of average<br>reaction |
|                            |                      |                               |                            |                              |                                   |                          |                              |                                   |
|                            | <i>per<br/>cent</i>  | <i>per<br/>cent</i>           |                            |                              | <i>mm.</i>                        |                          |                              | <i>mm.</i>                        |
| PPD-S. ....                | 1.20                 | 5.90                          | 97                         | 75                           | 23.1 x 21.1 x 2.4                 | 23                       | 19                           | 20.4 x 18.3 x 2.4                 |
| PPD-S1 (Hu-<br>man).....   | 0.35                 | 3.60                          | 97                         | 75                           | 23.7 x 22.6 x 2.5                 | 23                       | 19                           | 21.1 x 21.1 x 2.4                 |
| PPD-S. ....                |                      |                               | 66                         | 49                           | 37.7 x 34.9 x 2.7                 | 40                       | 29                           | 29.9 x 24.8 x 2.5                 |
| PPD-49609<br>(Human)...    | 1.70                 | 2.90                          | 66                         | 49                           | 37.0 x 34.9 x 2.7                 | 40                       | 29                           | 30.6 x 25.4 x 2.5                 |
| PPD-S. ....                |                      |                               | 17                         | 13                           | 21.2 x 21.2 x 2.3                 | 6                        | 4                            | 11.5 x 11.3 x 1.5                 |
| PPD-S2 (Bo-<br>vine). .... | 0.25                 | 0.68                          | 17                         | 13                           | 37.4 x 32.2 x 2.6                 | 6                        | 4                            | 16.8 x 16.0 x 2.0                 |
| PPD-S. ....                |                      |                               | 51                         | 43                           | 27.7 x 23.6 x 2.5                 | 10                       | 6                            | 17.9 x 17.4 x 2.2                 |
| PPD-S3<br>(Avian)...       |                      |                               | 51                         | 42                           | 17.3 x 13.4 x 1.8                 | 10                       | 6                            | 12.4 x 10.9 x 1.7                 |

in spite of the fact that the first preparation involved 3,664 cultures and the second only 100.

Furthermore, as shown in the original description (1) of the preparation and properties of PPD-S, a pilot lot designated No. 49609, prepared in the same way

and from the same strain, but on Dorset's instead of Long's synthetic medium, proved to have a similar degree of purity and equivalent potency (see table 1), in spite of the fact that a solution of this protein was dark brown as a result of the use of glucose in the medium. Three preparations of similar potency and purity have, therefore, been prepared already, and it seems probable that further comparable preparations could be made.

Preparations were then made in a similar way from a bovine strain, No. 523, and also from an avian strain, No. 6. Potency tests revealed the fact that the bovine product was much more potent and the avian much less potent than the PPD-S (table 1). These results confirmed those found earlier by Seibert and Morley (6), in which comparison was made on guinea pigs between products prepared from these strains by the trichloroacetic acid method. Probably the type of organism used is of importance, for Jensen and Lind (7) found no difference between tuberculin from human and bovine type bacilli when these were tested on guinea pigs infected respectively with these bacilli, whereas the tuberculin from avian bacilli was weaker except when tested in animals infected with the homologous strain. Lind and Tolderlund (8) found tuberculin from human type bacilli to be four times stronger in human beings infected with human or bovine type bacilli than a bovine type tuberculin made from BCG. Lind and Holm (9) found the mutual proportion of potency between the two tuberculins to differ according to whether the comparative tests were made on "naturally tuberculin-positive" subjects or on BCG vaccinated subjects.

No attempt was made to determine the exact relationship of the potencies of these three products, *i.e.*, the bovine and avian preparations and PPD-S, although this could be done by testing other series of patients in which the amount of the test product would be varied while the dose of PPD-S would remain constant. In this way tests on large numbers of patients of varying sensitivity to both first and second dose would seem to give a fair idea of the relative potencies of two products. In this clinic it would be difficult to administer six tests at a time to one patient as is done by the Danish workers (2).

#### CHEMICAL PURITY OF PPD PREPARATIONS

It should be emphasized that the products made by this procedure (1), *i.e.* isolation of the proteins from a heated tuberculin by means of ammonium sulfate precipitation at pH 7.0, are purer from the chemical standpoint than are those isolated by the earlier method of trichloroacetic acid precipitation (table 2). The electrophoretic diagrams in figure 2 show clearly an extra fast component, (marked with arrows) which appears in all the preparations made by trichloroacetic acid precipitation. As chemical purity is the goal in any such isolation, the ability to remove most of the 11 to 27 per cent nucleic acid and 20 to 28 per cent polysaccharide, which are inert substances in the tuberculin reaction (10), must be considered an advanced step in the purification. The resulting product, which is practically nothing but protein, can now be fractionated into its component proteins, at least three of which have so far been isolated in sufficiently pure form to be recognized as individual proteins. Until such time as these can

be isolated in really pure form, however, and it can be decided which one or ones are of greatest specific value in the tuberculin test, it is advisable to use for practical skin testing a preparation containing as many as possible of the proteins which exist in Old Tuberculin and are present in the original heated tuberculin used for these isolations. Such a product is the PPD-S.

TABLE 2  
*Analyses of different PPDs*

| PREPARATION OF PPD                      | NUCLEIC ACID    | POLYSACCHARIDE  |
|---|-----------------|-----------------|
|   | <i>per cent</i> | <i>per cent</i> |
| Precipitated with trichloroacetic acid: |                 |                 |
| PPD-98970.....                          | 21.9            | 25.8            |
| PPD-III a.....                          | 25.2            | 27.9            |
| PPD-III b.....                          | 27.2            | 23.6            |
| PPD- (Denmark 1939).....                | 20.0            | 24.0            |
| PPD- (Denmark PT-VII).....              | 11.0            | 20.6            |
| Precipitated with ammonium sulfate:     |                 |                 |
| PPD-S.....                              | 1.2             | 5.9             |
| PPD-81.....                             | 0.35            | 3.6             |
| PPD-49609.....                          | 1.7             | 2.9             |

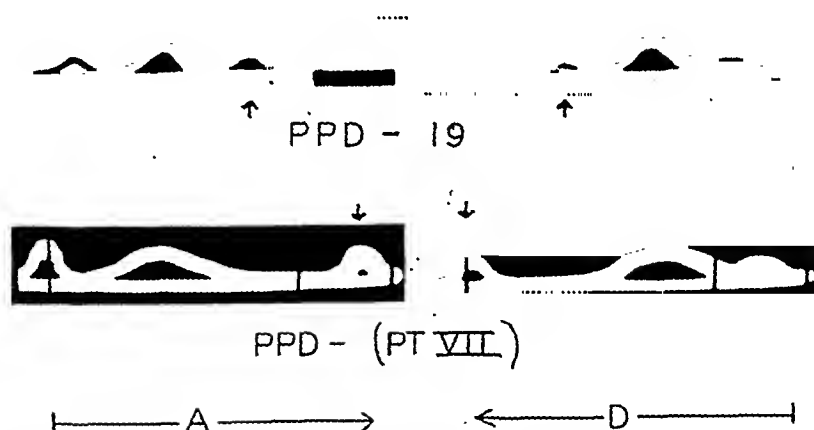


FIG. 2. Trichloroacetic precipitates

#### QUESTION OF SENSITIZATION WITH PPD

Obviously a fraction cannot be responsible for biological reactions beyond those caused by the whole original material from which it was isolated. If Old Tuberculin is nonsensitizing, a sensitizing substance should not be isolated from it, unless an inhibitory substance has been removed, and there is no indication of the presence of such a substance.

Steele and Willis (11) found that, if skin tests were repeated in children every two days, or at most every two weeks, until 20 tests were given, out of 85 children,

15 finally failed to react to PPD, 9 failed to react to Old Tuberculin, and 6 failed to react to TPT, a protein preparation from unheated tuberculin. Therefore, if these reactions indicate sensitization, practically as great sensitization occurred with Old Tuberculin as with the other products. As a matter of fact, the proteins in Old Tuberculin have some sensitizing power when sufficiently freed of the excessive impurities present so that they can be injected repeatedly in large quantities (12). Perhaps some antigenic capacity is necessary to elicit a reaction. With the amounts used for skin testing, however, the possibility of sensitization by repeated testing does not seem to be very great, as will be shown below.

In the course of studies made at the Henry Phipps Institute by Hetherington and Eshleman<sup>3</sup> on tuberculosis in a group of student nurses, tuberculin tests were routinely made by one of us (E. D.) in connection with clinical check-ups at three month intervals throughout the three year training course. Nothing except PPD-S has been used for testing since 1941. At practically every test period each nurse received two tests with the first dose, 0.00002 mg. PPD-S and, if negative at 48 hours, she received two tests with the second dose, 0.005 mg. PPD-S. These double tests were made because a record of the tuberculin reactivity to the standard tuberculin was required for the nurse's own clinical history, and a comparison was desired for standardization of various batches of PPD-S to be used by the U. S. Public Health Service. In this way, a nurse could receive as many as 48 tests in the course of her training if she remained negative throughout. As a matter of fact, only in the recent classes were there nurses who remained negative to tuberculin throughout their entire course. There were a few who remained completely negative during 30, 31 or more tests, but many who never became sufficiently sensitive to react to the first dose. It is obvious from a glance at the record of reactions that there is no trend toward sensitization which would be shown by a consistent increase in the degree of reactivity. The records are too voluminous to include in this paper. They have been analyzed and will appear as a separate communication (13). The conclusions reached in this careful statistical study were that the results of the analysis show no effect which may be plausibly construed as an increase in sensitivity due to tuberculin testing, although a small increase in sensitivity from this cause might pass undetected. In any event, it is certain that such increases, if they actually existed, were quite small relative to the natural fluctuation in response from test to test, and therefore are almost certain to be clinically unimportant. It appears, therefore, that repeated tests with PPD-S can be given at close intervals of time with no fear of complicating false reactions due to sensitization.

Among these recent classes of nurses, whereas relatively few of them developed sufficient sensitivity to react to the first dose, there appeared with the second dose (0.005 mg.) a fluctuation of sensitivity from negative to positive and back again many times during the whole training period. This same fluctuation among relatively less sensitive individuals was observed by Dr. J. D. Aronson<sup>4</sup>

<sup>3</sup> Personal communication.

<sup>4</sup> Personal communication.



when he reviewed tests on BCG vaccinated children. It was of further interest that he found this phenomenon in certain Indian reservations and not in others. He noted that the same phenomenon occurred whether he was using the earlier less pure triehloracetie precipitated PPD or the most recent and purest preparation PPD-S. In the study on the nurses mentioned above, "the data suggest, but do not prove, that the tendency toward increases of low sensitivity and decreases in high sensitivity over the year are more pronounced in the years in which exposure to infection was higher. . . . This gives no evidence against the hypothesis that these changes in sensitivity are, at least in considerable part, due to slight infection and gradual recovery" (13).

When clinically significant infection occurs, however, the individual usually reacts to the first dose (0.00002 mg.). The studies of Furcolow, Hewell and Palmer (14) indicate that 0.0001 mg. PPD-S may represent a critical dosage for detecting such cases, and consequently the disturbing phenomenon of fluctuation of sensitivity to the higher dose 0.005 mg. would be eliminated. The extensive studies of Palmer in progress at the present time may be able to answer some of these questions.

#### STANDARDIZATION OF TUBERCULINS

As guinea pigs are much less sensitive than human beings, a more accurate standardization of tuberculin can be made upon human beings, especially of products which are to be used for human testing. For this reason standardizations in this laboratory have all been made on human beings. Holm and Lind (5) reached the same conclusions. The following tests illustrate this point. In 1941, after PPD-S was prepared, standardization tests were made in guinea pigs and in man on the same products.

Guinea pigs rendered tuberculous by inoculation into the groin with 0.1 mg. H37 five weeks previously were used. Six dilutions of one product, ranging in dosage from 0.001 to 0.00025 mg. PPD-S, were given on one side of 6 guinea pigs while on the other side a series of six dilutions of another product was injected. In this way, the dilution which gave an average reaction equivalent to one of the known dilutions of PPD-S was found and the relative potency thus determined.

A large series of tests were then made in humans with the standard on one arm and the dosage of another tuberculin, judged to be equivalent by guinea pig test, on the other arm. If the average size reactions to the two tuberculin were not really equal, then another series of patients was injected with a smaller or larger dose of the tuberculin to be tested along with the same dose of standard. The results of the tests in man appear in table 3.

A summary of the tests in both man and guinea pigs can be stated as follows. When compared with 0.1 per cent PPD-S in six tuberculous guinea pigs, the 0.2 per cent PPD-S, 0.25 per cent PPD-98970, and an undiluted Old Tuberculin proved to be respectively 1 to 2 times, 0.5 to 1 times and 2.5 to 3 times as strong as the standard. In human beings, these products were respectively 2 to 3 times as strong, equal to, and five times as strong, as the standard. These figures

TABLE 3  
*Standardization of tuberculin in human beings*

| PREPARATION               | DOSE IN 0.1 CC.<br>mg. | DILUTION | NUMBER TESTED | NUMBER POSITIVE | DIMENSIONS OF AVERAGE REACTION<br>mm. | DOSE IN 0.1 CC.<br>mg. | DILUTION | NUMBER TESTED | NUMBER POSITIVE | DIMENSIONS OF AVERAGE REACTION<br>mm. |
|---------------------------|------------------------|----------|---------------|-----------------|---------------------------------------|------------------------|----------|---------------|-----------------|---------------------------------------|
| PPD-S (0.1 per cent)..... | 0.00002                | 1:5,000  | 51            | 33              | 27.2 x 24.3 x 2.6                     | 0.005                  | 1:20     | 16            | 13              | 21.2 x 19.3 x 2.2                     |
| PPD-S (0.2 per cent)..... |                        | 1:6,400  | 51            | 33              | 20.5 x 26.8 x 2.7                     |                        | 1:25.6   | 16            | 13              | 22.2 x 19.9 x 2.2                     |
| PPD-S (0.1 per cent)..... | 0.00002                | 1:5,000  | 43            | 33              | 25.9 x 22.3 x 2.3                     | 0.005                  | 1:20     | 7             | 5               | 13.0 x 11.4 x 2.7                     |
| PPD-S (0.2 per cent)..... |                        | 1:10,000 | 43            | 33              | 26.2 x 22.0 x 2.3                     |                        | 1:40     | 7             | 5               | 15.4 x 12.4 x 2.7                     |
| PPD-S (0.1 per cent)..... | 0.00002                | 1:5,000  | 60            | 45              | 20.3 x 23.2 x 2.3                     | 0.005                  | 1:20     | 15            | 12              | 16.9 x 15.3 x 2.0                     |
| PPD-S (0.2 per cent)..... |                        | 1:15,000 | 60            | 45              | 26.3 x 23.3 x 2.3                     |                        | 1:60     | 15            | 12              | 15.7 x 14.5 x 2.0                     |
| PPD-S (0.1 per cent)..... | 0.00002                | 1:5,000  | 46            | 35              | 25.6 x 22.5 x 2.6                     | 0.005                  | 1:20     | 7             | 3               | 23.0 x 18.6 x 2.0                     |
| PPD-S (0.2 per cent)..... |                        | 1:3,325  | 46            | 35              | 27.1 x 23.3 x 2.6                     |                        | 1:13.3   | 7             | 3               | 23.3 x 19.0 x 2.3                     |
| PPD-S (0.1 per cent)..... | 0.00002                | 1:5,000  | 54            | 37              | 22.8 x 20.6 x 2.4                     | 0.005                  | 1:20     | 19            | 11              | 17.5 x 14.5 x 1.9                     |
| PPD-S (0.2 per cent)..... |                        | 1:5,000  | 54            | 37              | 23.2 x 21.1 x 2.4                     |                        | 1:20     | 19            | 11              | 15.6 x 13.5 x 1.8                     |
| PPD-S (0.1 per cent)..... | 0.00002                | 1:5,000  | 57            | 43              | 26.3 x 22.4 x 2.5                     | 0.005                  | 1:20     | 19            | 14              | 16.2 x 14.3 x 1.9                     |
| PPD-S (0.2 per cent)..... |                        | 1:12,500 | 57            | 44              | 28.2 x 24.5 x 2.5                     |                        | 1:60     | 19            | 14              | 17.6 x 16.1 x 1.9                     |
| PPD-S (0.1 per cent)..... | 0.00002                | 1:5,000  | 31            | 23              | 25.5 x 22.7 x 2.7                     | 0.005                  | 1:20     | 6             | 3               | 17.0 x 16.3 x 2.3                     |
| PPD-S (0.2 per cent)..... |                        | 1:25,000 | 31            | 23              | 23.2 x 21.3 x 2.7                     |                        | 1:100    | 6             | 3               | 17.3 x 16.0 x 2.3                     |

are based on an average of 154, 100, and 88 tests, respectively, in these three series. It is obvious that the comparative results in human beings are in the same direction as those in the guinea pigs, but the differences in potency are magnified in the former, possibly because of the higher sensitivity of the human subjects.

It became clear in these tests that it is difficult to make an exact standardization of tuberculins prepared in different ways. For example, in the case of some preparations the relative potencies were different if tested in animals with different levels of sensitivity and even in groups of patients with different degrees of sensitivity. Thus, in some cases, as may be seen in table 4, one tuberculin (Old Tuberculin 511-10) may appear to be weaker than another (PPD-S) when tested in equivalent doses in highly sensitive individuals, and the same tuberculin may be stronger when tested in greater strength in less sensitive individuals.

TABLE 4  
*Relative potencies of different PPDs*

| PREPARATION | DOSE     | NUMBER TESTED | NUMBER POSITIVE | NUMBER MISSED | DIMENSIONS OF AVERAGE REACTION | DOSE   | NUMBER TESTED | NUMBER POSITIVE | NUMBER MISSED | DIMENSIONS OF AVERAGE REACTION |
|-------------|----------|---------------|-----------------|---------------|--------------------------------|--------|---------------|-----------------|---------------|--------------------------------|
|             | mg.      |               |                 |               | mm.                            | mg.    |               |                 |               | mm.                            |
| OT* 511-10  | 1:10,000 | 46            | 19              | 0             | 14 x 16 x 2.0                  | 1:100  | 27            | 17              | 0             | 18 x 20 x 2.2                  |
| PPD-20b     | 0.00002  | 46            | 19              | 0             | 21 x 22 x 2.4                  | 0.005  | 27            | 15              | 2             | 17 x 19 x 2.2                  |
| PPD-20b     | 0.00002  | 180           | 38              | 9             | 19.0 x 20.3 x 2.0              | 0.005  | 130           | 92              | 6             | 12.8 x 14.8 x 1.6              |
| PPD-S       | 0.00002  | 180           | 47              | 0             | 20.5 x 22.9 x 2.1              | 0.0025 | 130           | 96              | 0             | 14.6 x 16.6 x 1.7              |
| PPD-20b     | 0.00002  | 200           | 47              | 2             | 21.4 x 24.9 x 2.4              | 0.005  | 143           | 68              | 10            | 12.6 x 14.0 x 1.3              |
| PPD-S       | 0.00001  | 200           | 49              | 0             | 21.9 x 25.0 x 2.3              | 0.0025 | 143           | 78              | 0             | 13.0 x 15.3 x 1.3              |
| PPD-98970   | 0.00002  | 87            | 15              | 6             | 20.5 x 23.2 x 2.3              | 0.005  | 66            | 25              | 9             | 14.9 x 17.5 x 1.9              |
| PPD-S       | 0.00002  | 87            | 21              | 0             | 29.8 x 32.3 x 2.8              | 0.005  | 66            | 34              | 0             | 19.2 x 22.9 x 2.3              |
| PPD-98970   | 0.00005  | 26            | 20              | 0             | 26.9 x 30.5 x 2.5              | 0.02   | 18            | 7               | 0             | 17.9 x 19.4 x 2.3              |
| PPD-S       | 0.00002  | 26            | 20              | 0             | 24.4 x 27.5 x 2.5              | 0.005  | 18            | 7               | 0             | 18.9 x 21.4 x 2.4              |

\* Old Tuberculin.

Another difference that occurs between different tuberculins is in the total number of reactors. For example, PPD-S gave more total reactions with both doses than did PPD-20 b or PPD 98970, two lots of PPD which had been prepared by precipitation with trichloroacetic acid. McCarter and Watson (15) noted the same thing in their comparisons of PPD-S, and two other lots of PPD (PPD-67 and 67-2). Seideman (16) found a preparation of Old Tuberculin to be definitely more potent than PPD in the lower dilutions, whereas the PPD was found to be slightly more potent in the higher dilutions in guinea pigs. This investigator also found that in healthy young adults the initial dose of PPD (one-fifth of that found comparable to Old Tuberculin) was significantly more sensitive than that of Old Tuberculin, although the total number of reactors to Old Tuberculin was slightly greater as compared with PPD. He interpreted the facts to indicate a greater specificity of PPD as compared with Old Tuberculin.

That this interpretation may be correct is borne out by recent work, in which raw unheated tuberculin has been fractionated into at least three proteins distinguishable by different electrophoretic mobilities, chemical properties, biological potencies, and relative amounts in the tuberculin. These fractions have been designated as A, B and C proteins. They have been isolated on three different occasions and from two different strains of human type tubercle bacilli. They were identified by their different mobilities in electrophoresis and, while not completely homogeneous, they were sufficiently freed from the other proteins to warrant preliminary tests. The isolation procedures and analyses will appear in a separate communication. Skin tests were made in which each of these products was compared with PPD-S as a standard simultaneously on tuberculous guinea pigs and then on human subjects. In all cases equivalent amounts, based on the nitrogen contents, were injected in 0.1 cc. volume.

In the tests on guinea pigs, 0.1 cc. of the different substances was injected in the same guinea pigs and in this way the relative potencies could be determined. In the first experiment, by chance there were available three guinea pigs which had been vaccinated with 20 mg. of BCG eleven months earlier, and 5 guinea pigs that had been injected with 0.001 mg. DT strain five months previously. Twenty-four hours following the five skin tests with 0.005 mg. each of A, B, B-purified, C, and PPD-S fractions, all five of the tuberculous guinea pigs were dead and all three of the BCG guinea pigs were alive and presented moderate skin reactions. The unexpected severity of the reaction, suggesting the presence of a fraction of exceptionally high potency in this group, led to further comparative testing of the different substances. Tests were made using 0.0005 to 0.00026 mg. doses. In several series of tests, where only one product and the standard or where several products and the standard were tested on each guinea pig, it was clear that the A protein was more potent and the C protein less potent than the standard, while the B was intermediate.

Tests were then made on the more sensitive human beings with 0.00002 mg. and on the less sensitive ones with 0.005 mg. doses, comparing a single product with the standard in a large series of individuals. Table 5 shows that in all cases where the C protein was used considerably smaller reactions occurred than with the standard, and in some cases a few tests were lost with the C protein. Tests with the C Protein (92 I) indicated that it was less than one-tenth of the strength of PPD-S. In those individuals who required the second dose, or 0.005 mg. to react, however, the reactions with the C protein were as large or larger than with the standard, in spite of the fact that reactions were even missed in some cases.

In contrast, those fractions containing only the A+B proteins were, as a rule, stronger than the standard, as shown in table 6, on both first and second doses. The proportionality of potency in different dosages would indicate a more specific substance. The fact that different preparations varied in the ratio of their potency to that of the standard may possibly be explained by the fact that these preparations obviously differ in their degree of purity, as can be seen on the electrophoretic diagram. Three of them contained B protein as well as A. Furthermore, in the isolation procedure it became clear that the A and B

proteins exist in the smallest quantities and are the most difficult to separate as well as the most labile fractions. Neither A nor B has so far been isolated in more than small quantities in electrophoretically pure form, but obviously this is an imperative step.

TABLE 5  
*Polency of C Protein\**

| PREPARATION | TYPE OF PROTEIN PRESENT | DOSE    | NUMBER TESTED | NUMBER POSITIVE | NUMBER MISSED | DIMENSIONS OF AVERAGE REACTION | DOSE  | NUMBER TESTED | NUMBER POSITIVE | NUMBER MISSED | DIMENSIONS OF AVERAGE REACTION |
|-------------|-------------------------|---------|---------------|-----------------|---------------|--------------------------------|-------|---------------|-----------------|---------------|--------------------------------|
|             |                         | mg.     |               |                 |               | mm.                            | mg.   |               |                 |               | mm.                            |
| PPD-S       | All                     | 0.00002 | 10            | 6               | 0             | 25.0 x 25.0 x 2.3              | 0.005 | 11            | 10              | 0             | 22.1 x 17.2 x 2.3              |
| 92 I        | C                       | 0.00002 | 10            | 4               | 2             | 13.7 x 13.7 x 2.0              | 0.005 | 11            | 9               | 1             | 19.0 x 15.0 x 2.2              |
| PPD-S       | All                     | 0.00002 | 36            | 21              | 0             | 32.0 x 37.0 x 2.7              |       |               |                 |               |                                |
| 92 II       | C                       | 0.0002  | 36            | 20              | 1±            | 21.4 x 23.5 x 2.0              |       |               |                 |               |                                |
| PPD-S       | All                     | 0.00002 | 43            | 22              | 0             | 29.2 x 25.9 x 2.4              | 0.005 | 20            | 10              | 0             | 17.3 x 15.4 x 1.9              |
| 94 I        | C                       | 0.00002 | 43            | 22              | 0             | 23.6 x 25.9 x 2.4              | 0.005 | 20            | 10              | 0             | 16.6 x 19.2 x 1.9              |
| PPD-S       | All                     | 0.00002 | 62            | 32              | 0             | 26.5 x 30.6 x 2.5              | 0.005 | 27            | 19              | 0             | 21.9 x 24.1 x 2.2              |
| 95 I        | C                       | 0.00002 | 62            | 24              | 8             | 19.5 x 22.0 x 2.0              | 0.005 | 27            | 12              | 7             | 21.2 x 24.0 x 2.5              |
| PPD-S       | All                     | 0.00002 | 34            | 18              | 0             | 28.3 x 32.8 x 2.1              | 0.005 | 18            | 11              | 1             | 20.0 x 23.9 x 1.8              |
| 98 I        | C                       | 0.00002 | 34            | 18              | 0             | 21.4 x 23.5 x 2.0              | 0.005 | 18            | 11              | 1             | 19.5 x 22.2 x 1.8              |
| PPD-S       | All                     | 0.00002 | 69            | 56              | 1             | 24.2 x 29.0 x 2.4              | 0.005 | 17            | 14              | 0             | 14.4 x 16.6 x 1.8              |
| TPT-18E(A)  | C                       | 0.00008 | 69            | 44              | 12            | 15.3 x 17.2 x 1.9              | 0.02  | 22            | 15              | 4             | 16.9 x 18.5 x 2.0              |

\* Preparations 92 and TPT-18E(A) were made from the H 37 strain of tubercle bacillus, preparations 90, 94 and 98 from the DT strain, and preparation 95 from a BCG strain.

TABLE 6  
*Polency of A and B Proteins*

| PREPARATION | TYPE OF PROTEIN PRESENT | DOSE    | NUMBER TESTED | NUMBER POSITIVE | NUMBER MISSED | DIMENSIONS OF AVERAGE REACTION | DOSE  | NUMBER TESTED | NUMBER POSITIVE | NUMBER MISSED | DIMENSIONS OF AVERAGE REACTION |
|-------------|-------------------------|---------|---------------|-----------------|---------------|--------------------------------|-------|---------------|-----------------|---------------|--------------------------------|
|             |                         | mg.     |               |                 |               | mm.                            | mg.   |               |                 |               | mm.                            |
| PPD-S       | All                     | 0.00002 | 40            | 24              | 0             | 27.4 x 31.9 x 2.8              | 0.005 | 16            | 16              | 0             | 20.7 x 22.7 x 2.4              |
| 90 II       | A + B                   | 0.00002 | 40            | 24              | 0             | 30.2 x 34.6 x 2.8              | 0.005 | 16            | 16              | 0             | 23.1 x 25.7 x 2.4              |
| PPD-S       | All                     | 0.00002 | 40            | 27              | 0             | 24.4 x 24.4 x 2.5              | 0.005 | 13            | 10              | 0             | 16.6 x 18.7 x 2.1              |
| 94 II       | A + B                   | 0.00002 | 40            | 27              | 0             | 28.9 x 31.9 x 2.5              | 0.005 | 13            | 10              | 0             | 18.7 x 19.7 x 2.1              |
| PPD-S       | All                     | 0.00002 | 27            | 18              | 0             | 27.2 x 23.7 x 2.6              | 0.005 | 3             | 3               | 0             | 20.7 x 22.3 x 2.7              |
| 95 II A     | A + B                   | 0.00002 | 27            | 18              | 0             | 23.4 x 31.0 x 2.6              | 0.005 | 3             | 3               | 0             | 21.7 x 24.3 x 2.7              |
| PPD-S       | All                     | 0.00002 | 35            | 19              | 0             | 23.8 x 25.8 x 2.4              | 0.005 | 17            | 13              | 0             | 20.1 x 22.5 x 2.5              |
| 98 III      | A                       | 0.00002 | 35            | 19              | 0             | 23.5 x 25.9 x 2.4              | 0.005 | 17            | 13              | 0             | 21.7 x 25.0 x 2.4              |

The results so far reported indicate that the search for a more specific protein fraction of tuberculin may be rewarded, for the fractions obtained could be duplicated, using the same strain of tubercle bacilli as well as different strains. (See tables 5 and 6).

## SUMMARY

Progress in the purification of the active principle of tuberculin has been outlined. The method, including precipitation with ammonium sulfate at pH 7.0, yields a chemically more pure protein than the earlier trichloroacetic acid precipitation method. The contents of nucleic acid and polysaccharide are much lower.

Furthermore, products of constant potency can apparently be prepared from the same strain of tubercle bacilli by this method, as three comparable lots have already been produced.

A product similarly made but from a bovine strain was more potent and one from an avian strain was less potent than the standard purified tuberculin, PPD-S.

Evidence has been presented from repeated double tests at three month intervals on a group of nurses to show that a cumulative sensitization due to the tuberculin protein itself does not occur. A fluctuation is evident, however, in the degree of reactivity from negative to positive and reverse, in those nurses whose sensitivity was so low that they reacted only to the second dose of 0.005 mg. PPD-S.

The standardization of tuberculins prepared in different ways is often difficult because their relative potencies may vary in individuals with different levels of sensitivity. This indicates the presence of a less specific fraction admixed with a more specific one. As support for this interpretation, such fractions have actually been isolated from raw tuberculin. These experiments predict the preparation of a more specific diagnostic reagent.

## SUMARIO

*Estudio de Ciertos Problemas Encontrados en el Empleo de la Tuberculina Corriente.  
Fraccionación de PPD, Estandarización de las Tuberculinas y la Cuestión  
de la Sensibilización*

Bosquéjase el adelanto logrado en la purificación del principio activo de la tuberculina. La técnica, comprendiendo precipitación con sulfato amónico a una pH de 7.0, rinde una proteína químicamente más pura que la antigua precipitación con ácido tricloroacético. El contenido de ácido nucleico y de polisacárido es mucho menor.

Además, con esta técnica, pueden aparentemente prepararse productos de potencia constante, de la misma cepa tuberculosa, pues ya se han obtenido tres lotes comparables.

Un producto preparado en forma semejante, pero de una cepa bovina, resultó más potente, y otro de una cepa aviaria, menos potente, que la tuberculina purificada corriente, PPD-S.

Preséntanse datos derivados de dobles reacciones repetidas a plazos de tres meses en un grupo de enfermeras para demostrar que no ocurre sensibilización acumulativa debida a la proteína tuberculínica misma. Obsérvase sí fluctuación en el grado de reactividad, de negativa a positiva, y viceversa, en las enfermeras cuya sensibilidad era tan baja que sólo reaccionaban a la segunda dosis de 0.005 mg. de PPD-S.

La normalización de las tuberculinas preparadas de distintos modos resulta a menudo difícil porque sus potencias pueden variar en individuos dotados de distintos grados de sensibilidad. Esto indica la presencia de una fracción menos específica mezclada con otra más específica. En apoyo de esta interpretación, se han aislado tales fracciones de la tuberculina bruta. Estos experimentos predicen la preparación de un reactivo más específico para diagnóstico.

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# THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

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**Recovery Types in Pulmonary Tuberculosis.**—The purpose of this study was to determine clinically and radiologically how and when lung lesions heal in adult tuberculosis. Of 1,244 patients discharged from the preventive rest period required for insured patients in Chile, 405 (236 men and 169 women) who had been under observation one year or longer by the National Employees' Medical Department were taken for consideration. Ages varied from 15 to over 55 years, 88.5 per cent being in the 15-34 year period. The stage of the disease on admission had been minimal in 27.65 per cent, moderately advanced in 56.5 per cent and very advanced in 3.4 per cent. The remaining 12.3 per cent suffered from pleurisy. Radiologically, 39.7 per cent showed at the time of admission unilateral infiltration, 31.1 per cent bilateral processes, 16 per cent both unilateral infiltration and nodes, 3.9 per cent unilateral nodes and in 2 per cent the manifestations were undetermined. Of 307 who had the sputum examined, 58.95 per cent proved positive. About 80 per cent of apparently arrested cases on discharge had had from six to twenty-four months of preventive rest. The types of recovery were: complete resorption, 6.4 per cent; residual pulmonary, pleural or pleuropulmonary (but mostly pulmonary) scars, 93.6 per cent. Calcification was present only in 0.2 per cent. Recurrences occurred in 10.9 per cent in a period varying from three to sixty-six months, but mostly (77.2 per cent) within the first two years following discharge. Recurrences were in the original site in 75 per cent, elsewhere in 20.4 per cent, and in both locations in 4.5 per cent. The

desirability of re-examining these patients every two or three months during the first two years after discharge is emphasized.—*Formas de Curación de la tuberculosis pulmonar del adulto, Arturo Rodríguez, Felicindo Mendoza, Mario Zanolli & René Cárdenas, Ap. respir. y tuberc. Santiago, April-June, 1947, 12: 110.*—(A. A. Moll)

**Reactivation following Recovery in Pulmonary Tuberculosis.**—A study of the type of recovery and incidental factors was made in El Peral Sanatorium in Chile in 524 patients who had been discharged from April 15, 1938 to June 30, 1946 in an apparently or actually arrested condition. Both clinical and X-ray examinations were made periodically after discharge. On the completion of the study 358 patients (68.4 per cent) remained under observation. This figure is, however, deceiving, as the length of the follow-up period must vary considerably in such a group, and this will naturally affect the results. The chances of reactivation of the disease average 3.35 per cent per year. Sex, type of the disease (including extent and presence of cavitation) and type of treatment seemed to have but little influence on the probabilities of reactivation, the data not being sufficiently conclusive on any of these points. A thorough follow-up system is most important during the first year following discharge when the rate of patients failing to return for examination is as high as 20 per cent.—*Formas de Curación en la tuberculosis pulmonar en el adulto, Hospital-Sanatorio El Peral (Medical Staff), Ap. respir. y tuberc., Santiago, April-June, 1947, 12: 124.*—(A. A. Moll)



**Supplementary Aids for Classification of Residual Lesions.**—In a group of 68 tuberculosis patients with residual X-ray shadows and occasionally positive sputum, various methods were used to clarify the nature of the lesions present. Tomography disclosed in 12 cases the presence of active pulmonary lesions amenable to treatment. Bronchoscopy revealed in 13 of 40 patients bronchial lesions of a tuberculous nature. Bronchography showed in 30 of 52 parietal changes in the bronchial tubes adjoining the original pulmonary focus. While not definitely tuberculous, the residual pulmonary or tracheo-bronchial process in 18 of the 68 cases may still conceal small active foci which available examination methods fail to reveal. A residual condition may be properly labeled only after a careful X-ray and tomographic examination. If the sputum or the gastric contents are occasionally positive, the cause may be located through a bronchoscopic or bronchographic or X-ray study.—*El problema del tuberculoso bacilifero con lesiones radiológicas de aspecto residual, Medical Staff of Pulaendo Sanatorium (Rapporteur, H. Duran M.), Ap. respir. y tuberc., Santiago, April-June, 1947, 12: 140.*—(A. A. Moll)

**Hepatic Function in Tuberculosis.**—Along with chronic alcoholism, pulmonary tuberculosis is a frequent cause of fatty infiltration of the liver. There is no direct clinical evidence of significant liver damage in patients with chronic pulmonary tuberculosis however. A review of twenty-five years of studies reveals that considerable laboratory evidence of liver function disturbance has been found, but a critical study of these publications shows that the function tests used were non-specific and obsolete. A subsequent study in which testing was carried out with the two milligram dose of bromsulphalein showed some evidence of hepatic dysfunction. In 1942, by using the more sensitive 5 mg. per kilogram test, Kruger and Gerber found evidence of impaired function, especially in far advanced protracted disease. They examined also a series of 20 patients with

secondary amyloid disease and found significant retention of bromsulphalein in 18 patients, in contrast with a previous study showing dye retention in 2 out of 12 patients when the 2 mg. dose was used. The present authors felt that with further improvement in the form of the serial bromsulphalein test, and with the availability of other fairly specific procedures such as the intravenous hippuric acid test, the cholesterol ester determination, the cephalin cholesterol flocculation test and the determination of a series of chemical serum components related to liver function, a satisfactory study could be made. By means of these procedures hepatic dysfunction was demonstrated in a large percentage of cases. The serial bromsulphalein test showed the greatest number of positive results. Outstanding abnormalities were found in 2 patients with complicating myeloidosis.—*Studies of Hepatic Function in Pulmonary Tuberculosis, A. Hurst, H. M. Maier & S. A. Lough, Am. J. M. Sc., October, 1947, 214: 481.*—(G. F. Mitchell)

**Streptomycin.**—This report is based on the findings in 43 cases of pulmonary tuberculosis treated with streptomycin. Thirty six of these, observed for a minimum period of six weeks following completion of therapy, are considered in detail. All patients were on complete bed-rest and none received collapse treatment until at least ninety days following start of drug treatment. In the beginning, 18 patients received 3.0 grams daily in divided doses for 120 days. Subsequently, the period of treatment was shortened to forty-two days. Three patients received one gram daily for forty-two days. There were 18 patients with recent predominantly exudative disease with early cavitation. Nine manifested satisfactory early remissions; all had patchy or confluent pneumonic lesions which apparently had not caseated or excavated extensively. In 2 of the 9, the remission was followed by relapse within two months after completion of drug therapy. Six patients showed considerable improvement without full remission. In 3, with extensive caseation,

a rapidly progressive course followed a short period of improvement. In 7 of the 18, the disease has been apparently controlled for six months without collapse therapy. Five others have had successful collapse treatment; all would have been considered as poor risks prior to improvement under streptomycin. There were 18 patients with predominantly fibrocavernous pulmonary tuberculosis; of these, 3 attained cavity closure and sputum conversion during therapy. Four were rendered suitable for thoracoplasty. In 10, there was some temporary improvement followed by progression of the disease. In several of these, collapse therapy might have been feasible if it had been undertaken at the time of maximal improvement. Within one week of start of therapy, there was evidence of healing of ulcerative lesions of the larynx or bronchi in all 8 patients in which these were present. Healing was usually complete by the end of the second month. Tubercle bacilli could be cultured regularly from 23 patients during and subsequent to therapy. There was a striking correlation between the appearance of *in vitro* resistance and the duration of streptomycin therapy. Resistant bacilli were obtained in all but one of 11 patients who received streptomycin continuously for periods of seventy-five to 120 days. Resistant bacilli were observed in only one of 11 patients who received streptomycin for forty-two days. The majority of drug resistant strains appeared in the third month of treatment. *In vitro* resistance has not been observed to disappear and has persisted in 4 patients from whom bacilli could be cultured regularly a year after the start of drug therapy. In all 7 patients who continued to discharge bacilli during and subsequent to drug treatment, the tuberculous infection became actively progressive following the detection of resistant bacilli. In each case, the disease was thereafter completely uninfluenced by further administration of streptomycin and 4 went on to die. Postmortem studies of 2 patients revealed no unusual findings. Streptomycin therapy appears definitely to be a valuable adjunct in the treatment of pul-

monary tuberculosis. In all 43 patients, there was a measurable degree of objective improvement. The best results are to be expected in the early acute exudative types of disease. Healing under streptomycin treatment appears to follow the same course as natural healing. Chemotherapy might be expected to increase the number of apparent cures and possibly to shorten the time required for healing. The lower pH of tuberculous caseous areas may be a factor in diminishing the efficacy of streptomycin in this type of disease. Streptomycin treatment cannot be expected to result in the complete eradication of tubercle bacilli from all foci. There appears to be a definite relationship between *in vitro* and *in vivo* bacterial resistance. The administration of the drug for only forty-two days greatly lowers the incidence of drug fastness. Streptomycin is particularly valuable in increasing the number of patients in whom surgical therapy will be possible. The drug is properly used at present in cases of progressive moderately and far advanced pulmonary tuberculosis of recent origin and of predominantly exudative character. In fibrotic disease, the drug should not be used until timing has been considered in relation to the development of drug fastness and possible future surgery. Short, two-week courses of treatment are recommended for laryngeal and bronchial disease for symptomatic relief. In view of the neurotoxicity of the drug, its use is not advised in minimal disease or more advanced tuberculosis in which the outlook is favorable by conventional methods. Unnecessary use of the drug leading to development of drug fastness renders it useless for occasions when it may be seriously needed.—*Streptomycin in the Treatment of Tuberculosis: II. Pulmonary Tuberculosis*, C. Muschenheim, W. McDermott, Susan J. Hadley, Harriet Hull-Smith & Alice Tracy, *Ann. Int. Med.*, December, 1947, 21: 989.—(H. R. Nayer)

**Streptomycin in Hematogenous Pulmonary Tuberculosis.**—All other usual methods of treatment having failed, it was decided to try

streptomycin in a case, practically hopeless, of hematogenous pulmonary tuberculosis in a woman 32 years old. Both the sulfate and the hydrochloride salts were used as available, the average daily dose being 1.5 g. in six portions of 250,000 units each. Tolerance was perfect, with the exception of a slight local tenderness in the injection site, more marked with the hydrochloride. No acoustic manifestations developed. Bacteriological, clinical and radiological results were truly amazing in a 3-month period, with restored appetite, an 18 pound increase in weight, decreased sputum and improved breathing. The streptomycin treatment had to be discontinued then for reasons beyond control. The benefit obtained in this case dating back six years was so outstanding as to justify a trial of the drug in all cases of tuberculosis where other methods fail or cannot be applied.—*Estreptomycin, con particular referencia a su aplicación en la tuberculosis pulmonar hematógena*, P. A. Tapella, *Prensa méd. argent.*, August 1, 1947, 34: 1419.—(A. A. Moll)

**Streptomycin and Sulphetrone in Tuberculosis.**—In experimental studies, sulphetrone was found to be slightly more efficient than diasone or promine in controlling tuberculosis; no acute or chronic toxic effects were noted. It was decided to conduct studies on human beings using streptomycin alone and in combination with sulphetrone. Streptomycin was administered intramuscularly in doses of 0.2 to 0.4 g. every four hours. The daily dose of sulphetrone was 6 to 9 g., given orally; fluids were restricted to one and a half quarts daily. A total of 17 cases was treated, representing a variety of tuberculous lesions. Good results were obtained in one case of tuberculous meningitis, in which 2 mg. of heparin were also given intrathecally; in 4 other cases, where heparin was not used, streptomycin was ineffectual. Temporary improvement was obtained in cases of acute miliary tuberculosis, but later there were recurrences with fatal outcome. Two types of reaction were noted at necropsy in these

cases. The first represented healed tubercles in which no bacteria could be detected. The second consisted of young active tubercles showing no signs of repair and containing enormous numbers of acid-fast bacilli; these were probably the result of more recent dissemination. No beneficial effects were noted in chronic fibrocaceous pulmonary tuberculosis. The authors believe that streptomycin is contraindicated in these cases. Although there were too few cases, it was thought that the combination of streptomycin and sulphetrone gave better results than the former drug alone.—*Treatment of Tuberculosis with Streptomycin and Sulphetrone*, D. G. Madigan, P. N. Swift & G. Brownlee, *Lancet*, December 20, 1947, 2: 897.—(A. G. Cohen)

**Pneumothorax in Tuberculosis.**—In 1943, there was a long list of patients awaiting hospital treatment for tuberculosis. Many were suitable for pneumothorax. Accordingly, a new plan was tried. Patients were admitted for induction of pneumothorax. After the first two refills the patients were sent home and further treatment was given in the out-patient department unless there were complications. The records of the first 150 cases were reviewed. The observation periods ranged from twenty to thirty-three months. The results were considered successful in 82 cases, doubtful in 5 and unsuccessful in 63. In the entire series, 36.7 per cent of the patients became sputum free or negative. The fact that a project of this sort must be conducted by experienced physicians is emphasized.—*Artificial Pneumothorax*, A. Maclean & J. S. Gemmill, *Lancet*, January 31, 1948, 1: 173.—(A. G. Cohen)

**Collapse Therapy of Tuberculous Patients with Bronchial Asthma.**—Therapeutic pneumothorax is compatible with bronchial asthma if the latter can be controlled medically, and if pulmonary and cardiovascular function are at least fair. Four cases were successfully treated. Sojourn at high altitude where the air contains fewer allergens may have helped in these cases. Two other

tuberculous patients with bronchial asthma were treated with seven- and eight-rib thoracoplasty, and withstood the procedure well.—*Zur Kollapsbehandlung Lungentuberkuloser Asthmatiker*, W. Zeun, Schweiz. Ztschr. f. Tuberk., 1947, 4: 169.—(B. Gersl)

**Extrapariosteal Pneumothorax.**—This preliminary report concerns the first 6 cases of extrapariosteal pneumothorax. The indications for this type of procedure are seen in extensive bilateral involvement where the poor general condition precludes thoracoplasty and where the dimension and superficial location of the cavity render extrapleural pneumothorax very risky. Extrapariosteal pneumothorax obviates the opening of lymphatics and blood vessels, which are usually in a state of dilatation due to peripleuritis between parietal pleura and endothoracic fascia. After resection of a portion of the fourth rib the internal periosteum of the neighboring ribs is liberated in its entire extent, the internal intercostal muscles are pushed inward and a pocket is formed. The internal wall is composed of the fused visceral and parietal pleurae covered by the endothoracic fascia, periosteum and internal intercostal muscles. The external wall consists of the internal surface of the ribs and external intercostals. Before closure the periost is treated with formol. None of the cases showed subsequent infection of the pocket during the period of observation (which is only two to three months). In all cases a favorable effect on the cavities is reported (disappearance or considerable diminution in size). It is admitted that the postoperative follow-up is too short to permit further conclusions.—*Le pneumothorax extrapariosté, premiers cas et perspectives d'avenir*, L. Meyer & J. de Rougemont (présentés par M. Bariety), Rev. de la tuberc., 1947, 11: 380.—(V. Leites)

**Effusion Complicating Pneumothorax.**—During the last three years, in the Sanatorium El Peral in Santiago, Chile, there were observed 110 cases of serous exudate as a complication of artificial pneumothorax. The

unnamed authors follow a classification, in which they distinguish between (1) serous or sero-fibrinous, (2) purulent or seropurulent and (3) mixed purulent exudates. This somewhat arbitrary distinction has been found of great value for determining the therapeutic procedures to be followed. These have to be based on the microscopic aspects of the fluid and on the state of the underlying pulmonary lesion. In all cases of frank empyema the lung has to be expanded actively, rapidly and at once, regardless of the character of the parenchymal lesion. In addition, in mixed exudates, pleural lavages with antibiotics are given. In serous exudates, the treatment depends upon whether the pneumothorax is considered efficient for the treatment of the disease. Of the 110 cases with serous exudate studied, 61 were treated for an average of 3.1 months with lavages of physiological saline weekly or bi-weekly. The ultimate object was to cure the pleural complication and to preserve the pulmonary collapse. In 4 (6.5 per cent) cases a cure was so obtained. All other cases did not benefit from the treatment: 17 (27.9 per cent) for progressive symphysis, 22 (36.1 per cent) for persistent effusion, and 18 (29.5 per cent) for development of empyema. The therapy was then discontinued and active reexpansion of the lung was started. Where empyema developed, it did so in an average of 2.4 months from the beginning of the treatment for the exudate. In 21 of the 22 cases with chronic serous effusion the pulmonary expansion with consequent cure of the pleural complications was obtained in an average of 3.5 months, whereas in the group with purulent effusion (18) only 7 responded with a complete reexpansion. In 11 cases the expansion was partial only, and chronic encapsulated empyema persisted; 49 cases were treated with immediate reexpansion, as the collapse of the lung was inadequate. Of these, 21 developed a frank empyema, in 10 of which the lung reexpanded completely in an average of 5.5 months. The remaining 11 reexpanded partially only. Of the 28 serous exudates, 25 responded with total reexpansion

after 3.1 months of treatment; 3 did not re-expand. In both groups there was practically no difference in the final results. The average time required for reexpansion was much less in the serous than in the purulent cases. Furthermore, there is no significant difference between the transformation of serous fluid into empyema in the group with immediate active reexpansion (42.8 per cent) and the group in which maintenance of pneumothorax for therapeutic reasons was attempted (29.5 per cent). The repeated small traumas by aspiration and lavage, then, cannot be the cause for the empyema. There were 106 exudates examined for acid-fast bacilli; 402 by direct smear, 370 by culture, and 24 by animal inoculation. In 54 (50.9 per cent) tubercle bacilli were found. Of these, 40 fluids were found positive only after more than four examinations. An empyema ensued three times as often in those with tubercle bacilli in the fluid as in those without.—*Algunos aspectos de la evolucion de los exudados serosos que complican el neumotorax terapeutico, Bol. d. Hosp.-San. "El Peral," April-October, 1946, 6: 17.*—(W. Swienty)

**Clicking Pneumothorax.**—In some patients with a left pneumothorax, a clicking sound may be heard which is synchronous with the heart beat and is often audible at a distance from the patient; the author describes 2 cases in which this phenomenon was noted. In both cases, the sound persisted for many months after the pneumothorax had become well established; eventually it disappeared. Various theories of origin are discussed. The author believes that the sound is produced by the lingula being flipped against the anterior chest wall by the cardiac impulse. The sound was produced in this manner in a cadaver.—*Clicking Pneumothorax, W. Fox, Lancet, February 7, 1948, 1: 210.*—(A. G. Cohen)

**Artificial Pneumoperitoneum.**—One hour after induction of pneumoperitoneum for tuberculosis, the patient developed pain in the left groin. The scrotum soon became swollen

with air. This subsided in nine days, after which refills were continued. It is believed that the cause was a traumatic opening of an anomalous processus vaginalis.—*Scrotal Pneumocoele as a Transient Complication of Artificial Pneumoperitoneum, W. N. Rogers & J. V. Garrett, Brit. J. Tuberc., July, 1947, 41: 70.*—(A. G. Cohen)

**Pulmonary Congestion and Distensibility.**—The effect of pulmonary congestion on the distensibility of the lungs was investigated in both the isolated lung of the dog and in the open-chest animal. The degree of distensibility was derived from the corresponding increases in intratracheal pressure produced by inflation of the lung with known volumes of air and, in the isolated lung, also from changes produced by lung inflation upon the ratio of intratracheal to "intrathoracic" pressures (the latter being the pressure in the chamber in which the lung was enclosed). In the isolated lung, injections of known volumes of heparinized blood into the pulmonary artery resulted in a diminished distensibility of the lung. Withdrawal of this blood caused a return of the distensibility toward its control level, thus demonstrating that the decreased distensibility was due to intravascular blood rather than intraalveolar transudate. In the open-chest dog, compression of the pulmonary veins, producing pulmonary congestion, also resulted in a decrease in distensibility of the lung. Release of the compression caused a return of the distensibility toward its control level. Aortic compression, another method for producing pulmonary congestion, also diminished pulmonary distensibility. Improvement in pulmonary distensibility occurred after compression of the main pulmonary artery, after partial compression of both venae cavae, and during the development of shock toward the end of the experiment. This study demonstrated that the distensibility of the lungs varied in an inverse manner with the amount of blood in the pulmonary vessels. (Authors' summary.)—*The Effect of Pulmonary Vascular Congestion on the Distensibility of the Lungs,*

I. Mack, M. Grossman & L. N. Katz, *Am. J. Physiol.*, October, 1947, 150: 654.—(G. C. Leiner)

**Dissociated Paralysis of Diaphragm.**—Four months after a second right phrenic crush, supplemented by pneumoperitoneum, it was found that the anterior and mid-portions of the hemidiaphragm remained paralyzed and showed slight paradoxical motion; the lateral and posterior portions, however, had regained full function. At operation, no accessory fibers had been noted. The author believes that in this case, the fibers in the phrenic nerve were so arranged that one part was more thoroughly crushed than the other. This phenomenon has therapeutic implications. Since most tuberculous lesions are posterior, premature resumption of function of this position of the hemidiaphragm could have unfavorable consequences.—*Dissociated Paralysis of Diaphragm following Phrenic Crush and Pneumoperitoneum*, W. Fox, *Thorax*, March, 1948, 3: 15.—(A. G. Cohen)

**Pulmonary Emphysema.**—Pulmonary emphysema is a functional disease of the lungs in which there is marked interference with the diffusion of oxygen and carbon dioxide. When impairment in this function may be substantiated with symptoms and X-ray evidence of pulmonary emphysema, a definite diagnosis can be made. Without demonstration of impairment in diffusion of oxygen and carbon dioxide despite dyspnea and/or roentgenographic evidence of overdistention of the lungs, emphysema may only be conjectured. Symptoms of dyspnea may occur with normal lungs when ventilation is reduced. Similarly, overdistention of pulmonary segments, which may reduce ventilation, does not necessarily impair the interchange of gases. Bullae and blebs result from overdistention of alveoli near the pleural surface of the lung and may exist in otherwise normal lungs. Emphysema is not a necessary accompaniment of such phenomena. Overdistention of the lungs does not always bring about a loss of diffusion function;

in fact, there is little exact knowledge concerning what actually happens in lung tissues which causes impairment of its ability to diffuse oxygen and carbon dioxide. It is not known where emphysema is a primary or secondary disease. Nineteen case histories are given to illustrate the foregoing conclusions.—*A New Approach to the Understanding of Pulmonary Emphysema: A Method of Determining Emphysema of the Lungs*, G. G. Ornstein, *Quart. Bull. Sea View Hosp.*, April, 1947, 9: 89.—(P. Q. Edwards)

**Intrathoracic and Venous Pressures.**—Intrathoracic pressures are usually recorded from air pockets, the values depending on the amount of admitted air. Intrathoracic pressures can be recorded by calibrated optical capsules through air systems with the introduction of only insignificant quantities of air. Anesthetized dogs were used for these experiments. The following conclusions were reached: "Records of intrapleural pressure from the upper regions of the left side and lower regions of the right side of the thorax consist of smooth curves of subatmospheric pressure which decrease further during inspiration. Changes in these pressures are occasioned by modifications in tonus and contraction of respiratory muscles, blood content of the chest, and elasticity of lung tissue. Records from artificial pockets around the right heart and in the left lower pleural spaces adjacent to the apex of the heart show superposition of conspicuous cardiac variations on respiratory variations. It is suggested that these superadded variations rather than distortion of lung tissue by the heart and mediastinum are responsible for the existence of somewhat higher pressures around the heart than in the pleural cavities. In order to compare variable pressures around the heart with constant pressures found in some pleural leads special methods for comparison were devised. Of several methods tried, the comparison of instantaneous pressures at the end of a selected diastole, or so-called Z pressure, is an adequate and simple procedure which is easily related

to atrial pressures as well. Comparison of such Z pressures in various intrathoracic regions reveals that pressures recorded from the right lower thoracic cavity are only about 10 mm. H<sub>2</sub>O higher than those derived around the right heart and change directionally with them. Since it remains a moot question as to which of these more closely approximates the true intrathoracic component, such records may certainly be used in calculating trends of effective venous pressure. The error involved is no greater than exists in most of our biological data. Intrathoracic pressures recorded from the upper regions of the chest, from the whole left side or regions above the diaphragm and from the mediastinum, are unreliable for one reason or another."—*Regional Intrathoracic Pressures and Their Bearing on Calculation of Effective Venous Pressures*, C. J. Wiggers, M. N. Levy, & G. Graham, *Am. J. Physiol.*, November, 1947, 151: 1.—(G. C. Leiner)

**Blood Gases and Bronchial Asthma.**—The effect of a broncholytic spray ("Aleudrin," 1 per cent) has been tested by means of determination of arterial blood gases. Fifteen adult asthmatic patients were observed, 7 of them on two different occasions. The following measurements were obtained: vital capacity, arterial oxygen saturation, carbon dioxide content, carbon dioxide tension, blood pH, and alkali reserve. These figures were computed both before and after administration of the drug by nebulizer over a two-minute period. It was found that most patients initially showed a low vital capacity combined with undersaturation of oxygen. Whenever the spray treatment was successful in increasing the vital capacity significantly, increase in the oxygen saturation towards normal was observed. With regard to the carbon dioxide content, four different types of figures were encountered. One group showed lowered carbon dioxide content with lowered oxygen saturation, and one group showed nearly normal oxygen saturation with low carbon dioxide content. In both groups the alkali reserve was nearly normal. The lowered carbon di-

oxide content was due to hyperventilation in an effort to obtain better oxygen saturation. Treatment in these two groups raised the carbon dioxide level and the pH was slightly lowered. The third and fourth groups of patients demonstrated various degrees of compensated forms of acidosis. In the third group the oxygen tension was somewhat reduced, but the carbon dioxide tension was normal or somewhat raised. Treatment raised the oxygen tension, lowered the carbon dioxide tension, and raised the pH slightly. The fourth group showed considerable retention of carbon dioxide with markedly increased alkali reserve, diminished oxygen tension, and a nearly normal pH. Although this form of acidosis was still compensated, treatment was not successful in materially influencing the blood gas situation, although oxygen saturation increased somewhat. Presumably the situation in the lung was sufficiently pronounced and chronic so that not much benefit could be expected from antispasmodic treatment.—*Dcr O<sub>2</sub> und CO<sub>2</sub>—Gehalt des arteriellen Blutes bei Asthma bronchiale und seine Beeinflussung durch eine broncholytische Spray*, F. Verzar & W. Voegtti, *Schweiz. med. Wchnschr.*, September 18, 1947, 77: 980.—(H. Marcus)

**Nitrogen in Blood.**—The nitrogen content of arterial and venous blood was determined in dogs during inhalation of 99.6 per cent oxygen; the results were the same when the dogs were breathing a mixture of 5 per cent CO<sub>2</sub> and 95 per cent O<sub>2</sub>. The mean values at 0, 10, 20, 30, 40, 60, 180, 240, 300 and 360 minutes, respectively, were for arterial blood: 1.11, 0.28, 0.25, 0.22, 0.21, 0.21, 0.19, 0.16, 0.14, 0.12 volumes per cent; for venous blood, 1.12, 0.45, 0.39, 0.34, 0.31, 0.27, 0.24, 0.20, 0.19, 0.15.—*Nitrogen Content of Femoral Arterial and Venous Blood in Anesthetized Dogs Denitrogenated by Continuous Inhalation of 99.6 per cent Oxygen*, L. Karel & R. E. Weston, *Am. J. Physiol.*, November, 1947, 151: 71.—(G. C. Leiner)

**Cough as Symptom.**—Cough is dependent upon a local stimulus which originates nerve

reflexes through the medulla. The act of coughing can be divided into three phases: (1) the inspiratory phase, followed by (2) the compressive phase which depends upon the closure of the glottis and an increase in the intrapulmonary pressure, immediately preceding expiration, and (3) the expiratory phase, when the vocal cords and ventricular bands are quickly separated and air is forced out with the production of characteristic cough sounds. Purpose of cough is the removal of mucus, inflammatory exudate, and any other material in the air passages. The rôle played by bronchial movements during respiration is extremely important in the removal of secretions from the air passages. Deep inspiration increases the motion of the bronchial walls and this tends to move bronchial secretions. The degree of mobility is practically negligible during quiet respiration, such as is observed in narcosis, acute pleurisy, and injuries to the chest. Ciliary function is also important in the elimination of secretions from the air passages. It is more effective in the presence of thin than in thick secretions. Cough is a symptom, and the cause must be determined. This may be common respiratory tract disease, smoking, exposure to dust and fumes, extrapulmonary causes ("ear cough" or "reflex aural cough"), diseases of the nose and nasal accessory sinuses, nasal or pharyngeal obstruction, aspiration of food or fluid, and allergy. Cough of functional origin occurs, but one must be careful to exclude all possible organic causes before arriving at this diagnosis. To determine the exact cause of cough, careful history and physical examination are necessary. Examination of the ear, nose and throat, and chest, plus chest X-rays are usually indicated. Bronchography is indicated if there is any suspicion of increased bronchopulmonary markings suggesting bronchiectasis. In the presence of a history of allergy, appropriate tests must be performed. Treatment must be directed at the cause of cough. Cough is necessary to rid the tracheal bronchial tree of excessive secretions, for example, in pulmonary abscess or bronchiectasis, and, in these, narcotics should be used

sparingly, if at all. On the other hand, in carcinoma, cough is quite purposeless, and therefore symptomatic therapy and suppression of cough may be indicated. When cough is inadequate due to thick tenacious secretions, so-called stimulating expectorants are recommended. Inhalations of carbon dioxide and oxygen increase the quantity of sputum and have been highly recommended.—*Cough as a Symptom, L. H. Clerf, M. Clin. North America, November, 1947, 31: 1595.*—(L. Hyde)

**Thoracoplasty Survey.**—The results of 308 cases of thoracoplasty for tuberculous disease of the lung over a five-year period have been subjected to study. Best results have been obtained with unilateral involvement where the cavities were smallest and in the two age groups of 18 to 25 and 40 to 45. The majority of deaths was due to progression of the disease three weeks to one year postoperatively. The immediate mortality was 5.1 per cent within the first three days; the total mortality was 24.6 per cent, or 76 cases out of 308, corresponding to 11.0 per cent of a total of 668 operations. Worst results occurred in the group where pneumothorax had been tried and was complicated by a pleural effusion. The highest incidence of mortality remains in the group of contralateral pneumothorax patients. Concerning cavity size in relation to results, best results were obtained in the cases with the smallest cavities. In the 308 cases, 255 (82.7 per cent) were unilateral, of which 133 (50.9 per cent) were discharged as arrested, 32 (12.2 per cent) were improved, 28 (11.9 per cent) were unimproved, 6 (2.3 per cent) became worse and 56 (21.8 per cent) died. In the group of 53 patients with bilateral disease, 26 (49.0 per cent) were arrested, 4 (7.5 per cent) improved, 3 (5.6 per cent) became worse and 20 (37.7 per cent) died.—*Survey of Thoracoplastics at Sea View Hospital Over a 5-Year Period (1937-1942), B. Krynski, Quart. Bull. Sea View Hosp., April, 1947, 9: 144.*—(P. Q. Edwards)

**Thoracoplasty.**—All thoracoplasty cases from 1935 to 1946 were reviewed. These was



performed in various institutions and by different surgeons. A total of 633 cases were studied. Forty-five (7.1 per cent) could not be traced. Death occurred within four months in 17 (2.7 per cent) and later in 45 (8.7 per cent). Present fitness for work was found to be: full in 375 (59.2 per cent), light in 35 (5.5 per cent), unfit in 53 (8.4 per cent) and not recorded in 53 (8.4 per cent). No cases of tuberculous empyema are included. The usual cause of early death was atelectasis on the operated side followed by spread to the other side. Hemoptysis was noted occasionally. Later deaths were usually due to exacerbation of disease in the remainder of the lung or in the other lung or to nonrelated causes. The mortality to a large extent depends upon the type of cases selected. Most patients considered doing full work have light jobs. Sputum reports are available in 457 cases. Of these, 73 (16 per cent) remained positive. Cases with persistently positive sputum are not considered failures; bronchiectasis is a frequent source of bacilli. It is often difficult to determine cavity closure, even with the use of planigraphy. Nevertheless, cavities appeared to be closed in 91 per cent.—*The Results of Thoracoplasty in Pulmonary Tuberculosis*, T. H. Sellors, *Thorax*, December, 1946, 2: 216.—(A. G. Cohen)

**Treatment of Postpleuritic Tuberculosis.**—Cases of tertiary tuberculosis, including those without demonstrable cavity and others with cavities but with negative sputum, were subjected to apical thoracoplasty where inaccessible to pneumothorax. Four to five ribs were resected in one stage under local anesthesia. The results were superior to those obtained with conservative treatment.—*Behandlung der Diskreten, Fruhertiaren, Postpleuritschen Lungenspitzen-tuberkulose Durch Fruhzeitige Spitzenplastik*, W. Froehlich, G. deRham & S. Steil, *Schweiz. Ztschr. f. Tuberk.*, 1947, 4: 125.—(B. Gerstl)

**Scapulectomy and Thoracoplasty.**—In order to prevent the development of extrapleural space infection following thoracoplasty, resec-

tion of one-half of the scapula is recommended. This should be done before the rib resection; it gives a better operative exposure, makes retraction of the scapula much easier and most of the trapezius and rhomboid muscles can be spared. Also, in case of very localized apical lesions, a one-stage thoracoplasty may then suffice; the upper three ribs are removed and enough of the fourth and fifth to allow for bedding in of the remainder of the scapula. With this technique, no patients developed extrapleural space infections. Once the space has become infected, scapulectomy is difficult to perform and does not produce the desired results.—*Scapulectomy and Thoracoplasty*, A. J. Coello, *Brit. J. Tuberc.*, October, 1947, 41: 75.—(A. G. Cohen)

**Resection in Pulmonary Tuberculosis.**—Twenty-nine cases of pulmonary resection for tuberculosis during the past five years have been reported from the Mayo Clinic. Indication for resection was bronchostenosis in almost half of the patients. All patients were either those in whom the usual collapse measures had failed or whose lesions were not likely to respond satisfactorily to various surgical collapse measures. The immediate surgical mortality rates were low: 2 deaths in 15 pneumonectomy cases, none in 14 lobectomy cases. Late deaths from extensive spread were one each in the 2 types of resection. The use of streptomycin in the immediate preoperative and early postoperative periods to protect against spread has been encouraging. Development of streptomycin resistance imposes a serious limitation in the usefulness of the drug in controlling late spreads. Nineteen of the 29 patients reported in this series are clinically well with negative sputum, 4 are dead and 5 have active lesions. One patient is untraced. Ulceration in the bronchial stump is not a serious complication. This has occurred in 3 patients with preexisting bronchial tuberculosis and in each case was responsible for positive sputum postoperatively. In 2 cases the ulceration responded promptly to local treatment with silver nitrate or intramuscular streptomycin and in the

third it has been kept intermittently active for a year by a silk suture in the bronchus. In view of the poor results that are anticipated with thoracoplasty in these patients, the results of this series seem to justify the conclusion that resection has an important place in the treatment of pulmonary tuberculosis.—*Resection in Pulmonary Tuberculosis*, O. T. Clagett & W. D. Seybold, *Proc. Staff Meet., Mayo Clin., February 18, 1948*, 23: 81.—(P. Q. Edwards)

**Calcified Pulmonary Foci.**—A total of 1,476 children were examined. Of these, 1,050 were contact cases and 426 were examined because of symptoms. The examination consisted of a patch test followed, if negative, by an intracutaneous test. X-rays were taken in 1,100 cases. Calcifications were seen in 105, of which 18 were in the lung, 21 in the lymph-nodes and 66 in both. The right lung was involved twice as often as the left. Only one had a negative intracutaneous test. No children under 2 years of age showed calcification; there was a progressive increase in incidence above that age. The contact children showed a higher percentage of calcification than the noncontacts. It was concluded that intrathoracic calcification in the population studied indicates *per se* a past tuberculous infection.—*Calcified Foci within the Thorax of English Children*, B. C. Thompson, *Thorax*, March, 1948, 3: 43.—(A. G. Cohen)

**Bronchial Tuberculosis.**—Bronchoscopy has contributed definite and useful data to our knowledge of tuberculosis of the bronchial tree. According to Derscheid and Touissaint, it spreads principally by way of the sub-mucous lymphatics. We know now that tracheobronchial tuberculosis may be primary or secondary. The former is rarely accompanied by active pulmonary lesions. The latter, according to most statistics, complicates pulmonary tuberculosis in 10 to 30 per cent of cases. The lesions most commonly found, in order of their development, are: (1) submucous infiltration with thickening, hyperemia

and granular aspect of the mucosa; (2) ulceration; (3) cicatricial stenosis or fibrosis. All three types of lesion are, in most cases, found only by the bronchoscope. The existence of bronchial tuberculosis may be suspected from the presence of "wheezing," of sonorous râles or of laryngeal crepitations. They suggest narrowing of the respiratory passages. The presence of tubercle bacilli in rather abundant sputum with absence of pulmonary lesions as indicated by auscultation and X-ray examination suggests bronchial tuberculosis. Hypo-ventilation of the lungs, more or less temporary, may be due to atelectases of greater or less extent from plugging of narrowed bronchial tubes by thickened mucopurulent secretion. Febrile episodes, without apparent cause, sometimes have their origin in bronchial lesions. The author reports three cases in some detail. The first was a typical example of primary bronchial tuberculosis which was quite extensive while the pulmonary lesions were limited. The bronchial lesions became cicatrised but did not entirely prevent the passage of air. The general state of the patient improved after large doses of vitamins A and D were given. The prognosis in this case was considered questionable. In the second case the bronchial lesions were secondary to extensive pulmonary disease. The right lung had become completely atelectatic. Pain behind the sternum in this case was relieved to some extent by pneumothorax on the left side. No attempt was made to dilate the constricted right bronchus by bougies, a procedure which the author considers unsafe and ineffectual. The third case was at first mistaken for one of asthma, and was not recognized as tuberculous for two years. In the mean time parenchymal involvement had occurred. The stage of cicatrization of the bronchial lesions had already been reached. In conclusion the author states that the prognosis of bronchial tuberculosis is always questionable and depends on two factors: first, the degree of evolution of the bronchial lesion which in certain cases is progressive toward a fatal outcome, and secondly, the amount of healing of cicatricial

stenosis that has occurred. The presence of bronchial tuberculosis always makes decision as to the advisability of collapse therapy somewhat difficult. It is contraindicated in primary bronchial tuberculosis as it renders the probability of complete stenosis more certain. If ulcerative parenchymal lesions dominate the clinical picture it may be used,

but with less prospect of success than if the bronchi were not involved. The results of local treatment of bronchial lesions with adrenalin, nitrate of silver or electric coagulation have, in the author's experience, not been entirely convincing.—*La tuberculose bronchique*, A. Gyselen, *Rev. belge de la tuberc.*, No. 3, 1947, 38: 208.—(A. T. Laird)

# PULMONARY AFFECTIONS OF OCCUPATIONAL ORIGIN<sup>1</sup>

RUTHERFORD T. JOHNSTONE<sup>2</sup>

## INTRODUCTION

The shadows cast upon the roentgen film, if incorrectly analyzed, may, figuratively speaking, grow into a dark and inescapable cloud overshadowing the mind of the patient whose films have been misinterpreted. Probably no phase of roentgenographic interpretation is as frequently inaccurate as that of the chest films of the industrial worker. There seems to be a tendency, indeed even a desire, on the part of the inexperienced physician to read into the chest films of those exposed to chemicals or dusts certain pathologic findings which are not actually present. Many a worker with a healthy chest has been told that he has some sort of an "osis." A few scattered calcified nodules or a minimal increase of the perivascular markings are often given unwarranted emphasis, and the workman is induced to withdraw from a good job. The situation recalls the admonition of Pancoast, who once remarked "Let's not talk about the normal chest. . . . We probably see normal chests only in children. . . . Let's speak about the healthy chest."

There is an old axiom that the diagnosis of pneumoconiosis is dependent upon the roentgenographic findings. While it is true that roentgenography constitutes the final step, the tendency to base the diagnosis of an occupational pulmonary disease upon chest films alone is apt to lead to erroneous conclusions, as will be exemplified in subsequent illustrations. In the diagnosis of pulmonary affections of occupational origin in each individual case, experience in radiology must be combined with knowledge of pathology and physiology and familiarity with the chemical properties of the alleged offending agent. With the introduction of new chemicals into industrial processes and with the recently discovered adverse reaction of the lungs to certain silicates, it seems opportune that this whole subject should be brought to the attention of the general practitioner, the radiologist, and the "chest specialist."

## DIAGNOSIS

In the approach to the diagnosis of pulmonary affections of occupational origin, the following points must be considered.

*History:* In no other phase of medical practice is the complete history of the patient's lifetime employment as important as it is in occupational medicine. The physician must elicit with meticulous insistence each and every activity the workman has engaged in since he left school. An illustration of this point is afforded by a case known to the writer of a patient whose signs and symptoms

<sup>1</sup> NOTE: This review was prepared at the request of the late Doctor Pinner. Some of the material and illustrations are taken from the author's recent book, *Occupational Medicine and Industrial Hygiene*, C. V. Mosby Co., publishers. [The Editors]

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indicated that he had bronchial asthma. A history was obtained to the effect that the man was currently working as a baker and had been so engaged for the past six years. The history further revealed that for two years prior to being a baker he had been an apartment house manager. Roentgenograms showed moderately diffuse fibrosis with evenly scattered nodulation of the lungs. In reporting the case to the Industrial Accident Commission of California, the physician correctly attributed the asthma to sensitivity to flour dust, but in ascribing the fibrosis and nodulation to the same agent he was definitely in error. Had a competent history of employment been obtained at that time, it would have yielded the information that from 1919 to 1939 the patient had been a hard rock miner, and, as such, had been exposed to free silica, the cause of fibrosis and nodulation.

*The nature of the alleged offending substance:* The case briefly described above also serves to illustrate the necessity of appreciating the potential harmfulness, or the relative inertness, of any given substance to which a workman has been exposed. It must be recognized whether a dust or chemical is an irritant, a corrosive, or an allergen. Inert substances must be differentiated from noxious agents, and free silica must be distinguished from the silicates.

The vast majority of all substances found within an industrial environment cause no appreciable harm to the pulmonary tissue. Regarding the industrial chemicals, the physician should learn to classify these according to the physiological reaction which they call forth, namely the asphyxiants, the irritants, and the anesthetic gases. The asphyxiants pass through the lungs without causing damage, but attack other systems of the body. The irritants affect the upper respiratory tract and only rarely the lungs. Most substances in the anesthetic group, after being inhaled, affect the central nervous system, the liver or the kidneys. A considerable number of chemicals may produce anemia.

Ammonia, which is an irritant, will cause intense congestion and swelling of the upper respiratory passages. The effect may be so severe as to cause death from spasm, or edema of the larynx. If, however, the patient survives, there may be little or no serious consequences, as the deeper structures have not been affected. Phosgene, or nitrogen dioxide, on the other hand, will cause either no, or only insignificant, irritation to the upper respiratory passages, but these gases may induce pneumonia or edema of the lungs through their action upon the alveoli.

Likewise, the oxides of metals, when inhaled, vary in their action. Lead oxide does not harm the lungs, whereas cadmium oxide or certain forms of beryllium may produce a profound chemical pneumonitis. The correct evaluation of these peculiar reactions will prevent unwarranted assumption in the diagnosis.

Recently a recognized internist referred a case to the writer, accompanied by some roentgenograms and a note which stated, "... the bearer, after working some years in a lead mine, has developed lead poisoning. He has not responded to treatment although the X-rays reveal heavy deposits of lead." The referring physician had been deceived by the word 'lead' in the occupational history. He should have known that lead is not deposited in the pulmonary tissue to become

recognizable on the chest films. Actually, the patient had advanced silicosis (figure 1). This example may seem exaggerated, but it is nevertheless true and illustrates the point that, unless other related factors are also taken into consideration, the roentgenograms may become a diagnostic pitfall.

Concerning the harm which is apt to result from the inhalation of industrial dusts, consideration must be given to the factors of weight, particle size, and concentration, as well as to the chemical nature of the dust. It is not amiss to

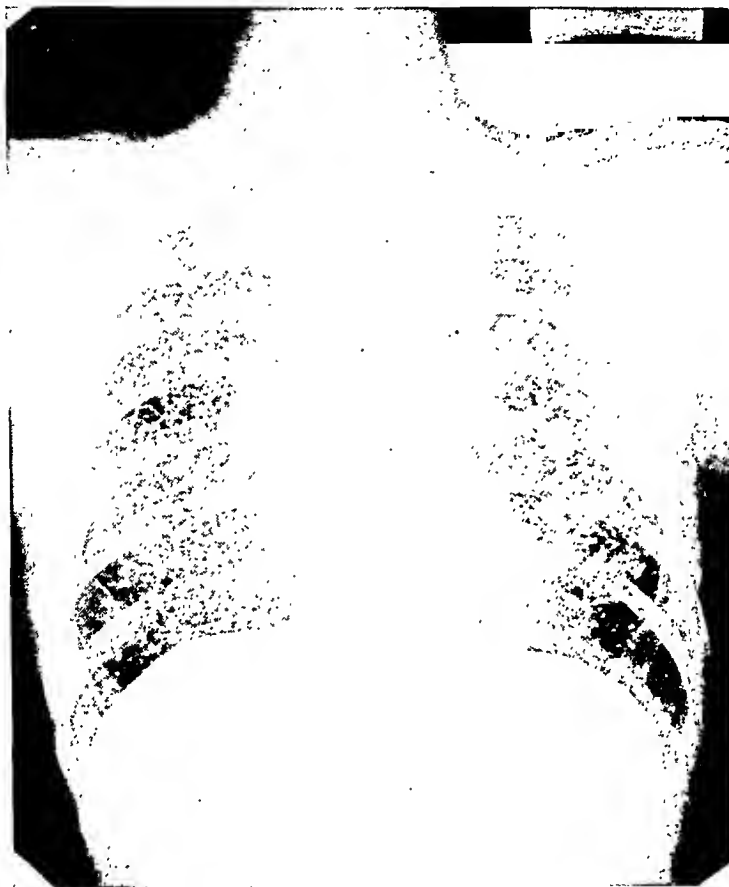


FIG. 1. Far advanced silicosis with tuberculosis. Films reveal marked fibrosis, diffuse, fuzzy nodulation, and areas of conglomerate nodulation, especially in right upper lobe.

point out that for a dust to be inhaled it must be extremely light, so light that it floats or remains suspended in the breathing zone of the exposed worker. It must be minute in size and highly concentrated. Because it fails to meet these qualifications, the ordinary dust is unable to pass the protective mechanism which nature has provided.

*The factor of inertness:* If, however, a dust does get by nature's protective mechanism to enter the lung, its chemical properties determine the reaction which it will call forth. The majority of all inhaled substances are chemically

inert within the pulmonary tissue. Therefore, unless an inhaled substance is capable of setting up a proliferative fibrosis, no harm will result. Herein lies the great difference between free silica and asbestos, and other dusts. (Chemical pneumonitis will be given separate consideration.) As the majority of all dusts are incapable of causing any appreciable fibrosis, they have been designated as benign. A benign pneumoconiosis is a condition wherein there may be some insignificant fibrosis, but never true nodulation. It causes no symptoms, no disability, and does not predispose to tuberculosis.

Despite the fact that the term "benign pneumoconiosis" is well understood by the experienced physician, its indiscriminate application is regrettable. The suffix "-osis" is confusing and conjures up a parallelism with silicosis. The innocent markings of a benign pneumoconiosis frequently lead to the assumption that a healthy chest is in fact a diseased chest, a mistake referred to in the opening paragraph of this article. Because of the frequency of this confusing error, the distinction between benign pneumoconiosis and disabling fibrosis should be clearly pointed out. The inert or benign dusts will therefore be briefly discussed prior to the consideration of certain harmful industrial dusts. As the inert dusts are legion, only a very few of them can be mentioned here.

### Iron Dust

Inhalation of iron dust will, after a number of years, produce a pigmentation within the lungs and on the lung surfaces, recognizable on the roentgenograms. This change, termed siderosis, causes a radiological pattern more nearly simulating silicosis than that of any other inert dust. Yet the picture of uncomplicated siderosis is sufficiently distinctive to make it discernible from silicosis. The pigmentation marks are round, sharply defined, and widely distributed throughout the entire lung fields. In siderosis, the hilar shadows are not enlarged, no confluent nodulations are apparent, and the shadows *remain unchanged* after years of implantation. These pigment deposits do not produce any reactive fibrosis. Sander (1) compared the innocuousness of iron pigmentation in the lungs to tattoo pigmentation in the skin. In siderosis, the light behind the film in the view box gives a certain brilliance to the discrete nodules, whereas in silicosis the nodulation is fuzzy and dull in appearance.

A case which came to the attention of the author will serve to emphasize the previously made contention, that it is necessary to consider other factors rather than to attempt a diagnosis based on roentgenograms alone. A male, 28 years of age, had been a grinder for seven years. Roentgenograms taken at the time of his physical examination for military service produced findings which caused his rejection, although he was in excellent health and free of symptoms. He sought the advice of his physician, who informed him that he had silicosis. Alarmed, he requested a change of position, a demand which led to his being referred to the insurance carrier's doctor and to several other consultants. Each time the diagnosis was that of silicosis. No attempt was made to evaluate his working exposure. When this was finally done, an analysis of the dust in the atmosphere showed it to contain 65 per cent iron oxide. No free silica was found

in the air analysis, nor did the grinding substance or the material being ground contain silica. An X-ray diffraction of the material also failed to disclose any silica. In figure 2 may be seen a chest film of the patient taken in 1943. In figure 3 may be seen a roentgenogram taken in 1946. It will be noted that the pattern remained unchanged in the two films, although they were taken several years apart.



FIG. 2

FIG. 3

FIG. 2. (Left) Siderosis. Film reveals diffuse, sharply defined, round and discrete pigmentations. No reactive fibrosis present. Film taken 1943.

FIG. 3. (Right) Siderosis. Film of same patient as shown in figure 2. After three years (1946) there has been no change in the X-ray markings (allowance is to be made for the factor of a different technical development of the two films).

### Cement Dust

Cement dust has been chosen for discussion because it illustrates so well the inertness of a very common dust. The writer examines semiannually the workers in a Southern California cement industry. Many of these, men as well as women, have worked many years for the company. Not once has there been a case which revealed any significant degree of pneumoconiosis, even though these individuals work without protective respirators. In figure 4 may be seen the chest film of a Mexican male who has worked for this company for 22 years, yet whose roentgenograms fail to disclose any evidence of significant pulmonary changes.

At the request of the Portland Cement industry, the Saranac Laboratory, under the guidance of the late Leroy Gardner, conducted in 1935 a survey among cement workers which was reported in its entirety only in 1939 (2). Over two thousand workers were examined, 70 per cent of whom had been employed for



periods varying from ten to fifty years. Of the roentgenograms, 82.06 per cent showed no abnormalities of any kind, 17 per cent revealed a certain degree of linear exaggeration. Further analysis indicated that about one-half of this group had been exposed to dusts other than cement prior to being employed in the cement industry. No nodulations were seen in the films of those workers who had been exposed only to cement dust.

The Saranae Group also investigated the relationship between dust exposure and the susceptibility to tuberculosis, bronchitis, and pneumonia. From their

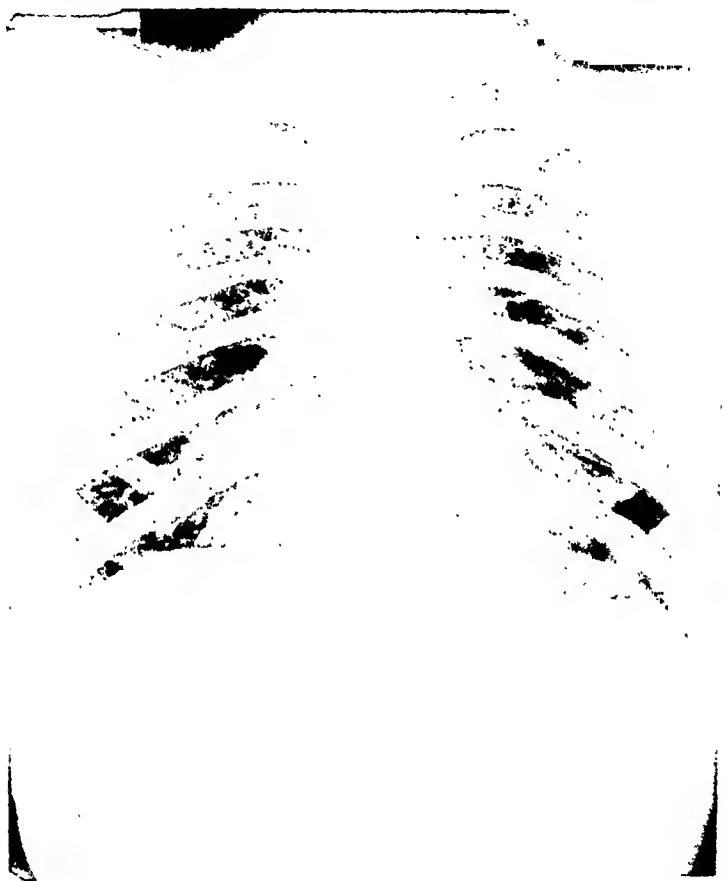


FIG. 4. Film of worker exposed to cement dust for twenty-two years. Slight increase of perivascular markings but otherwise negative film.

study it was concluded that prolonged inhalation of cement dust does not render the workers more susceptible to tuberculosis, pneumonia, or bronchitis, and that the incidence of these diseases is no greater among cement workers than in the general population. The conclusion that cement dust is harmless is equally applicable to most other inert dusts.

#### Cotton Dust

Cotton dust is a benign dust which produces no appreciable fibrosis, but is capable of being allergenic. Byssinosis is a peculiar respiratory affection result-

ing from the inhalation of cotton fibers and is characterized by the signs and symptoms of asthma and bronchitis. The writer reported such an instance in 1941 in the book, *Occupational Diseases* (3). In cases of prolonged exposure to cotton dust, recognizable fibrosis is noted. The cause of the pulmonary disturbance, however, is a fungus or mold identified as *aerobacter cloacae*. After investigating the cotton mills of England, Collis (4) concluded that occasional severe epidemics of coughing among the workers were due to mildew and molds, and that these molds were *Penicillium glaucum*, or *Aspergillus glaucus*.

### Bagassosis

Bagassosis is a term applied to a syndrome resulting from exposure to bagasse, the residuum of sugar cane after the sugar has been extracted. The substance is used in the manufacture of insulating boards. In the process, bales of bagasse are crushed by machinery with the evolution of much fine, dry dust.

After several months of exposure to this dust, men develop rather suddenly a cough productive of a foul-smelling sputum, dyspnea, and often retrosternal pain. This condition continues for several months after removal from exposure, but eventual recovery takes place. It is believed that the cause of this pulmonary disturbance is due to an antigen in the bagasse. No definite roentgen picture has as yet been established.

### Fiberglas

Fiberglas (wool glass, mineral wool, etc.) is a comparatively recent industrial product and information regarding its action upon the lungs has not yet found its way into the general medical literature. The name and the physical appearance of this substance are such as to lead workers and physicians to believe that it is bound to be harmful to the lungs. Chemically, this material contains no free silica and its physical characteristics render it non-respirable. Because of the impression created by early erroneous ideas about the harmfulness of fiberglas, extensive animal experimentation was carried out and numerous surveys of exposed men were conducted. These all revealed no evidence of pulmonary damage.

### Other Inert Dusts

Lack of space forbids the consideration of other industrial dusts such as carbon, calcium carbonate, magnesium carbonate, tobacco, sugar, and a myriad of others which are encountered in an industrial environment. Grain or malt dust, for instance, could be mentioned as the cause of a peculiar condition known as "grain fever." Here again, work in the grain industry by itself produces no appreciable fibrosis, but there often occurs a foreign protein reaction similar to that found in metal fume fever. New workers, or those beginning a new season, are frequently affected during the first few days or weeks of exposure.

In closing the discussion on the inert dusts, it is hoped that one point has been thoroughly appreciated, namely, that these dusts have been designated as inert because they fail to produce any appreciable degree of fibrosis. While it is not to be denied that on the chest roentgenograms of those exposed *in terms of years*

there will frequently be noted a slight increase of the perivascular markings, or even minimal fibrosis, it should be made quite clear that this condition is not disabling, never progresses to true nodulation, and that it does not lead to disabling fibrosis.

### Silicates

Silicosis and asbestosis are not included in this article as the readers of this journal are familiar with the various aspects of these diseases. It should be mentioned, however, that within the past few years the profession has been startled by reports of a disabling pneumoconiosis occurring in men exposed to certain silicates which heretofore were considered inert.

### Bauxite

Bauxite is hydrous aluminum oxide. The inhalation of aluminum dust has heretofore never been considered harmful to the lungs. Reports from the Aluminum Company of America indicate that its workers have been exposed to varying degrees of concentration of this dust over a period of many years without evidence of any significant pulmonary damage. In recent years, the use of aluminum powder or dust in the prevention and/or treatment of silicosis has been enthusiastically advocated by some investigators, although many authorities have voiced considerable doubt as to its effectiveness. This is not the place to enter into this controversy, but it can be said that seemingly no harm has resulted from the prophylactic or therapeutic use of aluminum powder in nontuberculous workmen.

In 1942, C. G. Shaver, Superintendent of the Niagara Peninsula Sanatorium, noted an unusual pulmonary condition in a 33-year-old male who for eight years had been working as a furnace tender in a nearby bauxite plant. The patient was not seriously ill, but roentgenograms disclosed a "peculiar shadowing and a pneumothorax." At first, his occupation was not considered relevant to the findings. Although it was believed that the changes were due to an infective process, the patient did not react to tuberculin and sputum tests as well as cultures failed to reveal the presence of tubercle bacilli or any other recognized disease-producing organism. Several months after observing the first patient, two additional cases came to the attention of Doctor Shaver. These two men displayed diffuse shadowing and bilateral pneumothorax. No more cases were seen until 1944, when three additional workmen presented the same syndrome. It was then that Doctor Shaver enlisted the aid of Doctor Riddell and Doctor Cunningham, of the Industrial Hygiene Division of the Department of Health, of Ontario, Canada, for a survey of the bauxite industry.

In the process of manufacturing abrasive material, bauxite is mixed with iron, coke or coal, and other ingredients, and then shoveled into large pots. This mixture is subjected to a temperature of two thousand centigrades, when large carbon electrodes are lowered into the pots. During this process, dense white fumes are evolved which, despite the existing exhaust system, escape to some extent into the atmosphere inhaled by the furnace tenders, crane operators, and

other workers in the immediate vicinity of the furnaces. Analysis of the fume showed it to contain 60 per cent alumina and 25 per cent silica, together with small amounts of inert material.

In the neighborhood of Niagara (Canadian side) four different companies are engaged in the manufacturing of this abrasive. A survey of these plants revealed that of the 1,913 individuals employed, only 344 were exposed to the fumes as they came from the electric furnaces. Examination of this group disclosed that 35 workmen showed definite radiological evidence of this strange pulmonary disease, while 13 others were classified as doubtful. Seven deaths had occurred. Not included in these figures is another group of workers, designated by the investigators as "early."

The symptoms of this entity, which has been termed "Shaver's Disease," vary with the intensity of the pulmonary involvement. Early cases may present only slight complaints or even no complaints at all. Invariably, the patients had noticed some degree of dyspnea prior to consulting a physician. A productive cough was also a rather early symptom. Sudden attacks of breathlessness caused most of the patients to seek medical advice. Those suffering from an advanced stage of the disease complained of substernal pain, or of a tightness in the chest, weakness, fatigue, and sleeplessness.

In the general physical examinations of the earlier cases, Shaver and his group had noted no abnormal physical symptoms. The chest signs were variable and largely depended upon the presence or absence of pneumothoraces. In those with a considerable degree of pneumothorax the chest expansion was limited, the percussion note showed impaired resonance over areas where the diaphragm had been elevated, whereas over the pneumothorax the percussion note was hyperresonant. Breathing was usually rapid and difficult, the breath sounds hoarse, and rales and rhonchi were invariably present. Prior to the roentgenological discovery of pulmonary symptoms, tachycardia and cyanosis, in conjunction with substernal pain, had in some instances led to the mistaken diagnosis of heart disease.

Roentgenographic studies revealed certain findings common to the entire group. The diaphragm was irregular, tented, and frequently elevated; the mediastinal shadow was expanded. There was a lace-like granular, bilateral shadowing of the lungs, more pronounced in the upper halves of the fields. Coarser shadows were noted in the more advanced cases. Emphysematous changes and ring-like shadows characterized the advanced group. Distinct blebs were seen on the pleural surface of the collapsed lung (figures 5, 6, 7, 8, 9). Doctor Shaver and Doctor Riddell point out that not one of the cases which had developed pneumothorax had developed a secondary infection in the pleural cavity, nor did any case demonstrate radiological evidence of complicating tuberculosis.

Four cases came to autopsy. The lungs cut with considerable resistance and dense fibrous tissue was found to have invaded the lung substance. The fibrosis was more intense in the upper and middle portions of the lung fields, and appeared to fan out from the lung roots towards the periphery. Emphysematous changes

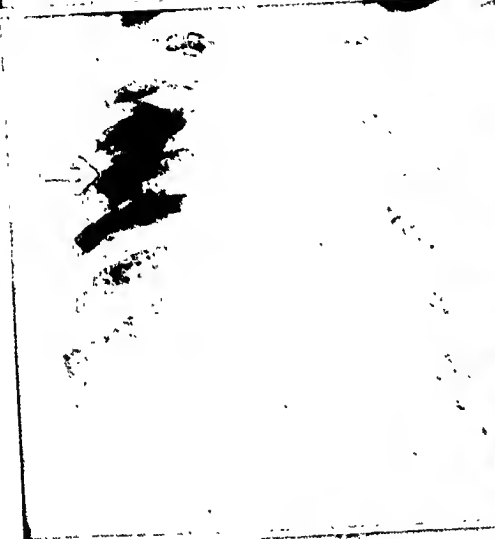
FIG.



FIG.



FIG. 9  
384



5

Fig. 7

were scattered throughout and occasional small cavity formations were seen. No evidence of caseation or tuberculosis was encountered in any of the specimens. Microscopic studies showed profuse fibrous tissue formation, alveolar wall thickening, and marked emphysema. The fibrosis was interstitial in type and involved the interalveolar septa.

### Diatomaceous Earth

The diatomaceous earth utilized for industrial purposes is acicular or needle-like in its formation. After being processed for industrial application, it is fluffy, exceedingly light and, because of these qualities, it is widely used as filters, fillers, and absorbents. The rubber, plastic, and fireproofing industries in particular have recognized its value.

Crude diatomaceous earth is obtained by quarrying or open pit mining. After removal, the earth is sent to a mill where, by a special drying process, all moisture is removed. The material is handled with great care so that the diatoms may be separated from each other without destroying their individual structure. Then the separated diatoms are conveyed by air stream through a system of cyclones, traps, and kilns, and finally packed for shipment.

For many years it has been assumed that in the diatomaceous earth industry workers do not develop any disabling fibrosis. This assumption was based on the belief that workers were exposed to an amorphous silica and not to the crystalline form. Some years ago, however, Leroy Gardner at Saranac carried out experiments with diatomaceous earth and found that his animals developed silicotic nodules which, at first, he was at a loss to explain. At that time analysis of the raw material had to be carried out chemically. Later, when the X-ray diffraction method was employed, he found that, if diatomite is calcined with certain fluxes, a portion of the amorphous silica is converted into cristobalite, a crystalline silica which is the potent cause of silicosis. Upon making this discovery, Gardner believed that his original experiments had been made with calcined diatomite and had therefore caused the silicotic reaction.

Subsequent experiments by Gardner with raw diatomaceous earth failed to produce fibrosis of the lungs. These studies were carried out with the amorphous form of silica. He then injected a calcined form, containing about 25 per cent cristobalite, and produced nodular fibrosis. Following his laboratory studies,

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FIG. 5. (Upper Left) Film of bauxite furnace tender taken July 1943. Both upper lobes show moderate fibrosis with slight bilateral pneumothorax of the bases.

FIG. 6. (Upper Right) Bauxite. Same worker as shown in figure 5. Showing complete collapse of right lung. Taken December 1943.

FIG. 7. (Centre Left) Bauxite worker. Film taken of same worker May 1944. Showing almost complete collapse of right lung with a faint shadow of a bleb on the pleural surface. Peak like tenting of right diaphragm.

FIG. 8. (Centre Right) Bauxite worker. This is of a different patient than previous figures. It likewise reveals collapse of right lung with large emphysematous bleb. Left lung shows marked fibrosis tissue with a pleural bleb.

FIG. 9. (Lower) Bauxite. This film is of a third worker, which reveals considerable collapse of the right lung with basal fibrosis and marked deformity of diaphragm. Left apex collapsed, fibrosis and granular like shadowing on the left.

Gardner came to California in 1945 to make a further study of the diatomaceous earth industry. He conferred with physicians and consultants engaged in caring for the men who worked with this substance, reviewed a collection of chest roentgenograms, and examined some of the workers. He later reported "silicosis is conspicuous by its absence." He did note an appreciable amount of benign, nonspecific pneumoconiosis, "as one would expect to find in any group exposed for a period of time to any dust."

Despite Gardner's belief in the innocuousness of diatomaceous earth, developments in the past year or two strongly indicate that fibrosis with nodulation has occurred in some instances of exposure to calcined diatomaceous earth. In subjecting the amorphous earth to high degrees of heat, it is believed that a crystalline silica is released and that such an exposure is able to produce fibrosis, nodulation, and disability. The action of heat upon the diatomaceous earth appears to produce certain changes similar to those noted in bauxite workers. Definite conclusions have not as yet been formed, however, and further study is obligatory before a final verdict can be pronounced.

The findings noted among bauxite workers, and possibly also among those working with diatomaceous earth, indicate that we may have to reconstruct our thinking regarding the inertness of certain of the silicates. It would appear that these silicates remain comparatively harmless until they are subjected to high temperatures. Experimental evidence is available to the effect that amorphous silicas will yield cristobalite when sufficiently heated. Bailey (7) showed that diatomaceous earth, which originally in his sample contained "a trace of cristobalite, 2 per cent quartz, and a few per cent of feldspar," also yielded cristobalite when heated at 1150 to 1200 C., especially in the presence of flux. Bailey indicates that with certain fluxes, such as sodium chloride, the conversion of amorphous silicas to cristobalite may take place at even lower degrees of temperature. Tridymite has also been found in the converted substance. This factor of conversion by heat, therefore, confronts industry with a great hazard and one that demands better control measures than are now practiced. It is believed that in the pottery, ceramic, and refractory industries heat could produce disproportionately large amounts of cristobalite, and even tridymite. Both of these substances are apt to cause silicotic reaction much more rapidly than quartz.

In addition to the industrial dusts which have been cited in this article, a few metals are capable of producing unusual pulmonary pathology. In a previous paragraph it was stated that the majority of chemicals, if inhaled, will not affect the lungs. This is particularly true of the metals as a group. Attention is called, however, to two exceptions.

### Beryllium

An unusual and puzzling pulmonary affection has been noted in the past few years among those exposed to beryllium compounds. Reports from Italy, Germany, and Russia indicate that a strange form of pulmonary disease has occurred in industries where beryllium had been used in some form. In 1943, Van Ordstrand (8) and his coworkers at the Cleveland Clinic noted the occur-

rence of a chemical pneumonia among workers engaged in extracting beryllium ore. At about the same time, Shilen and his coworkers (9) in Pennsylvania, reported a similar respiratory disturbance, and Hyslop et al., of the U. S. P. H. S. (10) concluded a study of the toxicity of beryllium and its acid radicals. Among others to report their observations of the disease have been Kress and Crispell (11) and Hardy and Tabershaw (12).

Beryllium is a rather rare element, although it is widely distributed in small quantities in feldspar and mica. In a few localities it occurs as beryl, a beryllium aluminum silicate. Beryl is the chief source of beryllium and beryllium compounds used in industry. It readily alloys with other metals.

As yet no uniform name has been adopted for the disease. It was called berylliosis by Fabroni. Others have called it beryllium sarcoidosis, or pulmonary granulomatosis, while a majority have merely designated the condition as a delayed chemical pneumonitis resulting from beryllium exposure. It is equally uncertain whether it can be attributed to the beryllium salts. It is now believed by most authorities that the disease stems from exposure to the acid radicals of beryllium, such as the fluorides and oxyfluorides.

*Clinical Features:* A study of the various reports reveals that there does not seem to exist any relationship between the length of exposure and the time of onset of the disease, nor does the intensity of exposure seem to constitute a factor. In some instances the contacts were casual, intermittent, and of brief duration. In a personal communication Gardner wrote: "Certainly we have no reason to believe that the tissue reaction is directly proportional to the intensity or duration of exposure." In a group of 17 cases reported by Hardy, 4 developed symptoms after a long period of employment in a common environment; a second group developed symptoms between three and eighteen months after leaving work, and a third group became ill as late as two or three years after cessation of exposure. Hardy was of the opinion that respiratory infection very often plays a part in producing the onset of beryllium intoxication.

The symptoms of intoxication from beryllium or its acid radicals include weakness, loss of weight, shortness of breath, anorexia, and a cough which usually is not at first productive. With progression of the disease, dyspnea usually becomes marked and cyanosis is present. In some patients the gastro-intestinal symptoms may be more disturbing than the respiratory difficulty. In the physical examination of those affected with this delayed chemical pneumonitis, cachexia is invariably noted, the breathing is rapid and shallow and the heart rate accelerated. Auscultation of the lungs is not likely to reveal significant changes. In later phases of the disease, rales may be heard in the bases or axillae. In one case of the writer's experience, a pleural friction rub was heard. Some observers have encountered enlargement of liver and spleen. Van Ordstrand found in his group of cases a high incidence of contact dermatitis, as well as ulcers from splash burns. He also reported a chemical nasopharyngitis and a chemical tracheobronchitis among the furnace tenders exposed to beryllium.

In the differential diagnosis it is essential to exclude miliary tuberculosis by laboratory studies. Boeck's sarcoid, although it presents some similarity in the



roentgenograms, can be eliminated by the occupational history as well as by the course of the disease. The roentgenograms may simulate silicosis, but the abrupt and early clinical onset of beryllium pneumonitis is not present in silicosis. Clinically, this chemical pneumonitis may simulate cardiac decompensation until roentgenographic studies are made. Likewise, it is not uncommon to find these patients referred to tuberculosis sanatoriums for diagnostic study. It is worthy of note that in subsequent laboratory investigations the blood counts and sedimentation rates remain fairly normal and that no elevation of temperature occurs until the terminal stage. No bacteriologic evidence of tuberculosis has



FIG. 10

FIG. 11

FIG. 10. (Left) Beryllium. Patient exposed to fluorescent powders. This shows finely granular and well distributed, particulate markings which cannot be called nodules at this stage (Aug. 12, 1946). Patient's illness took place six months previously. Condition stationary. Has polycythemia, slight clubbing of fingers, and fairly marked pulmonary insufficiency. (Courtesy Willard Machle, M.D.)

FIG. 11. (Right) Beryllium. Patient exposed to fluorescent powders and phosphorus. Case is of two years' standing. Tuberculosis was first suspected, as was silicosis of the acute type. Clinical condition improving. Can climb two flights of stairs without "blowing" and swims without evident dyspnea. (Courtesy Willard Machle, M.D.)

been found in these cases. Chemical studies of certain components of the blood were carried out in a small number of cases by Hardy, who encountered elevated globulin values which she attributed tentatively to the fact that delayed chemical pneumonitis might belong to the chronic granulomatous diseases.

*Roentgenologic Studies:* In the earliest stages a fine, granular, sandpaper appearance will be seen. There are no increased linear markings, no nodulation, no coalescence. The appearance is not smooth and homogenous, but distinctly particulate. It is also uniform and diffuse, extending to the periphery of the lungs and including the apices (figures 10, 11). In the second stage of the dis-

case, a diffuse reticular pattern on a granular background is seen. The hilar shadows become fuzzy. Consequently, distinct nodules appear uniformly throughout the lung fields. Small, fine areas of emphysema are also noted. There is no tendency for the nodules to coalesce, nor is any definite linear fibrosis apparent. The nodules remain fuzzy and do not calcify nor cavitate.

From the above it should be evident that the diagnosis of beryllium intoxication depends, first of all, upon the occupational history of an exposure; furthermore, upon the nature of the initial symptoms, the progression of the case; and, finally, upon the correct analysis of an unusual chest roentgenographic picture. The difference in the clinical course between the cases reported by Van Ordstrand and other observers is significant. In Van Ordstrand's group of cases, the onset was acute and, unless fatal, recovery, from the clinical as well as from the roentgenological point of view, took place after removal from exposure. In contrast, the majority of cases reported by other authors indicate a delay in the onset of symptoms and a progression of the disease after removal from exposure.

### Cadmium

The first death of an American worker resulting from cadmium intoxication was reported by the writer in 1941 (3). Previously, 15 cases of cadmium poisoning, including 2 fatalities, had been reported in the Canadian literature and, prior to that, Legge (13) in England reported a case of cadmium poisoning. In 1944, Spolyar (14) and his associates reported 5 cases of cadmium poisoning. These instances are individually enumerated to indicate that realization of the toxic effects of cadmium is, like those of beryllium, of fairly recent date.

Cadmium oxide, when inhaled, has probably more lethal potentialities than any other metal. The failure of industrialists to appreciate the toxic properties of this metal has caused workers to be unwittingly exposed to its fumes and has led manufacturers to incorporate it in products without proper warning of its presence. Like most metals, cadmium is innocuous in the cold state but, when it is subjected to high degrees of heat, its oxide is poisonous or even lethal upon inhalation.

The first symptom of cadmium intoxication is usually dryness of the throat, quickly followed by cough, headache and dizziness. After an interval of a few hours there occurs a characteristic constriction in the chest, accompanied by marked dyspnea. With an increase in the respiratory and cardiac rate, cyanosis is noted. Auscultation of the lungs reveals no abnormal findings; rales are conspicuous by their absence until the terminal stage of the disease. The roentgenograms show a surprising degree of widespread, patchy bronchopneumonia scattered throughout both lung fields, inconsistent with the auscultatory findings. At autopsy, edema and congestion of the lungs are noted, with occasional hemorrhage and partial collapse. A proliferative interstitial pneumonitis and catarrhal bronchitis are also present. All these changes are chemical in origin.

### Tuberculosis in Industry

During the recent war years mass surveys were conducted within industry, in order to detect the incidence of tuberculosis in the largest segment of our adult

population. These surveys were not made because it was believed that industrial surroundings foster tuberculosis, but rather because industry offers the machinery and opportunity for a more successful preventive health campaign than any community-sponsored program. We are not concerned here with that phase of the problem. We are concerned with the question as to whether exposure to the various dusts and chemicals of industry predisposes to tuberculosis or activates arrested tuberculosis.

Because an industrial environment is supposed to be dirty, grimy, and dusty, it has, out of ignorance, been accused of being an incubator for tuberculosis. Such thinking disregards vital components outside of the working environment of the employe, such as the economic factor, living conditions, congested housing, improper nutrition, financial insecurity with all its attendant worry, personal and community hygiene. Such thinking is an escape from the responsibility to provide our workmen with better homes, better and more abundant food, and more hours free from mental and physical strain. It is easier to blame a particular case of tuberculosis on an industrial dust, chemical, or humid atmosphere, than to place the responsibility upon our social and economic structure. Almost invariably the conditions within the four walls of the plant are better than they are down the street in the workman's home and community.

The statement that an industrial environment does not induce or aggravate tuberculosis is not an idle, thoughtless generalization. (The relationship between silicosis and tuberculosis is excluded from this portion of the discussion.) The effect of the occupational environment upon the incidence and production of tuberculosis has been given careful study over many years. It is a fact that nurses and medical students are often subject to contact with an open carrier and therefore their respective occupations constitute a hazard peculiar to their occupation. As far as all other occupations are concerned, the evidence is, by and large, to the contrary.

Lack of space does not permit a comprehensive discussion of the aforementioned statement. The reader is referred to the report of the Saranac Laboratory for the Study of Tuberculosis (15). That report contains the papers of men participating in the Symposium on Tuberculosis in Industry. All types of industrial exposures were surveyed, such as the various gases, solvents, metals, irritants, and dusts. The participants concluded that tuberculosis does not arise out of an occupational exposure to these substances. In summarizing the opinions expressed at that symposium, Leroy Gardner stated that "it was agreed that" exposure to fumes and gases could not be proved to favor the onset of tuberculosis; that neither lead absorption and intoxication, nor mill dust and foundry employment are associated with the development of tuberculosis. High temperatures and humidity are without significant influence upon tuberculosis, nor were any theoretical reasons advanced to the effect that they should be. Radiant heat in the steel industry causes no tuberculosis in those exposed.

#### SUMMARY

1. The actual incidence of pulmonary damage resulting from an exposure to the various industrial dusts and chemicals is rare.

2. Healthy adults reveal variations in the roentgenograms of their chests. Caution must be exercised in interpreting these variations of lung markings.

3. Minimal or even moderate fibrosis in itself is not disabling.

4. The majority of all industrial dusts are inert because they are incapable of producing a reactive, proliferative fibrosis. Even after years of exposure to these benign dusts, the resulting fibrosis is not progressive. It does not lead to disability or infection.

5. In estimating the possible effects of any given industrial substance, it is necessary to know its chemical nature.

6. It now appears that certain silicates which were once considered as inert may become noxious when subjected to high temperatures.

7. Certain metals, when subjected to high temperatures, liberate their oxides, which may produce chemical pneumonitis.

8. An industrial environment *per se* does not induce tuberculosis.

#### SUMARIO

##### *Neumopatías Ocasionadas por el Polvo Industrial*

1. La incidencia verdadera de las lesiones pulmonares debidas a la exposición a los varios polvos y productos químicos en la industria es rara.

2. Los adultos sanos revelan variaciones en sus radiografías torácicas, y hay que mostrar cautela al interpretar esas variaciones de las líneas pulmonares.

3. Una fibrosis mínima y hasta moderada no es de por sí incapacitante.

4. La mayoría de los polvos industriales son inertes por no poder provocar una fibrosis proliferante, reactiva. Aun tras años de exposición a esos polvos benignos, la fibrosis resultante no es evolutiva, y no conduce a incapacidad o infección.

5. Al estimar los posibles efectos de cualquier sustancia industrial dada, es necesario conocer su naturaleza química.

6. Parece ahora que ciertos silicatos considerados antes como inertes, pueden volverse nocivos al ser sometidos a temperaturas altas.

7. Ciertos metales, al ser sometidos a temperaturas altas, desprenden sus óxidos, los cuales pueden producir neumonitis química.

8. Un ambiente industrial no evoca, de por sí, tuberculosis.

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# STREPTOMYCIN IN PREPARATION FOR COLLAPSE THERAPY<sup>1</sup>

JOHN D. STEELE, JR., AND TIMOTHY R. MURPHY

## INTRODUCTION

The value of streptomycin therapy in patients with predominantly exudative pulmonary tuberculosis has been demonstrated adequately (1 to 8). Investigators agree that streptomycin in itself is rarely a definitive form of therapy but should be used as an adjunct to other treatment. D'Esopo and Steinhaus (9) suggest the use of streptomycin as an adjunct to collapse therapy.

Seventeen patients at Muirdale Sanatorium with pulmonary tuberculosis, which was predominantly exudative in character, were prepared rapidly with streptomycin for various collapse therapy procedures. The lesions of at least 13 of these were progressive when streptomycin therapy was started. The lesions of the other 4 patients, although not progressive or known to be progressive, were considered to be too recent and too exudative in character to permit the safe institution of collapse therapy. In the entire series the lesions were prepared for various collapse therapy procedures after an average of 78.8 days of streptomycin therapy. The actual period of therapy ranged from 44 to 140 days (see table 1). Without streptomycin it is extremely doubtful whether even the most favorable of these lesions would have been considered suitable for collapse therapy in less than six months. It is also doubtful whether most of the patients with progressive disease would ever have been considered suitable for collapse therapy, except possibly as a last resort procedure.

## COMPOSITION OF SERIES

Thoracoplasties were performed on 12 of the 17 patients; 3 had intrapleural pneumothoraces and 2 had extrapleural pneumonolyses. One of the latter was followed by paraffin filling and the other by lucite ball filling. In addition to these 17, temporary phrenic nerve paralyses were performed on 6 patients whose exudative lesions responded well to streptomycin therapy. The lesions of 3 of these patients were considered to have improved sufficiently on streptomycin therapy to permit the induction of intrapleural pneumothorax. The pneumothoraces had to be abandoned shortly after induction because of extensive, indissoluble adhesions and the phrenic paralyses were substituted. The lesions of the other 3 patients having phrenic paralyses responded so well to streptomycin therapy that no major collapse procedure appeared to be indicated, although it is entirely possible that they will require major collapse therapy after further periods of observation.

## OBSERVATIONS

The 17 patients being reported in some detail in table 1 and figures 1, 2, and 3 represent consecutive cases of major collapse therapy procedures instituted during the course of streptomycin therapy.

<sup>1</sup> From Muirdale Sanatorium, Milwaukee 13, Wisconsin, and the Marquette University School of Medicine.

TABLE 1

*Seventeen patients prepared for collapse therapy by the administration of streptomycin*

| CASE NUMBER<br>AND INITIALS | AGE | SEX | RACE | DOSE OF<br>STREPTOMYCIN               | NUMBER OF DAYS OF STREPTO-<br>MYCIN THERAPY PRIOR TO<br>INSTITUTION OF COLLAPSE<br>THERAPY | TOTAL DAYS STREPTOMYCIN<br>THERAPY | TYPE OF COLLAPSE<br>THERAPY                               | DISEASE PROGRESSIVE WHEN<br>STREPTOMYCIN THERAPY<br>STARTED? | REMARKS   |
|-----------------------------|-----|-----|------|---------------------------------------|--|------------------------------------|---|--|---|
| 1. G. R.                    | 20  | F   | W    | 2.0                                   | 95   | 162                                | Pneumothorax  | Yes  | Intrapleural pneu-<br>monolyses June<br>5, 1947 and July<br>7, 1947                                 |
| 2. E. D.                    | 26  | F   | W    | 1.0                                   | 65   | 184                                | Thoracoplasty<br>(8 ribs)                                 | No   |   |
| 3. T. P.                    | 17  | F   | W    | 1.0                                   | 88   | 211                                | Thoracoplasty<br>(10 ribs)                                | Yes  |   |
| 4. M. B.                    | 17  | F   | W    | 1.0                                   | 61   | 173                                | Thoracoplasty<br>(8 ribs)                                 | Yes  |   |
| 5. W. G.                    | 18  | M   | W    | 1.0                                   | 140  | 204                                | Thoracoplasty<br>(8 ribs)                                 | No   |   |
| 6. S. S.                    | 24  | F   | W    | 1.0                                   | 68   | 153                                | Thoracoplasty<br>(8 ribs)                                 | Yes  | Left phrenic pa-<br>ralysis following<br>thoracoplasty  |
| 7. T. S.                    | 29  | M   | W    | 1.0                                   | 83   | 196                                | Thoracoplasty<br>(10 ribs)                                | Yes  | Left pleural effu-<br>sion cleared with<br>streptomycin   |
| 8. E. B.                    | 20  | F   | W    | 2.0<br>(112 days)<br>1.2<br>(21 days) | 116  | 133                                | Extrapleural<br>pneumonolysis<br>with paraffin<br>filling | Yes  |   |
| 9. M. W.                    | 17  | M   | N    | 2.0<br>(73 days)<br>1.5<br>(75 days)  | 107  | 148                                | Pneumothorax  | ?  |   |
| 10. M. S.                   | 22  | F   | W    | 2.0<br>(60 days)<br>1.2<br>(75 days)  | 94   | 135                                | Pneumothorax  | Yes  | Intrapleural pneu-<br>monolysis De-<br>cember 11, 1947  |
| 11. E. M.                   | 19  | M   | W    | 2.0<br>(57 days)<br>1.2<br>(119 days) | 55   | 176                                | Thoracoplasty<br>(10 ribs)                                | Yes  |   |
| 12. E. K.                   | 34  | F   | W    | 1.0                                   | 59   | 142                                | Thoracoplasty<br>(6 ribs)                                 | Yes  | Previous tubercu-<br>lous empyema on<br>left  |
| 13. I. B.                   | 22  | F   | W    | 1.0                                   | 66   | 184                                | Thoracoplasty<br>(10 ribs)                                | No   | Severe stationary<br>ulcerative laryn-<br>gitis healed rap-<br>idly after strep-<br>tomycin started |

TABLE 1—*Concluded*

| CASE NUMBER AND INITIALS | AGE | SEX | RACE | DOSE OF STREPTOMYCIN                   | NUMBER OF DAYS OF STREPTOMYCIN THERAPY PRIOR TO INSTITUTION OF COLLAPSE THERAPY | TOTAL DAYS STREPTOMYCIN THERAPY | TYPE OF COLLAPSE THERAPY                       | DISEASE PROGRESSIVE WHEN STREPTOMYCIN THERAPY STARTED? | REMARKS   |
|--------------------------|-----|-----|------|--|---|---------------------------------|--|--|---|
|                          |     |     |      | gm.                                    |   |                                 |  |  |   |
| 14. V. K.                | 24  | F   | W    | 1.2                                    | 53  | 80                              | Extrapleural pneumonolysis with lucite filling | Yes  | Thoracoplasty refused December 23, 1947         |
| 15. B. C.                | 19  | F   | W    | 1.0                                    | 44  | 167                             | Thoracoplasty (10 ribs)                        | Yes  |   |
| 16. A. C.                | 54  | F   | W    | 1.5<br>(132 days)<br>0.75<br>(30 days) | 66  | 162                             | Thoracoplasty (8 ribs)                         | Yes  | Dose of streptomycin reduced because of vertigo |
| 17. R. B.                | 28  | F   | N    | 1.0                                    | 80  | 146                             | Thoracoplasty (6 ribs)                         | Yes  |   |
| Average..                |     |     |      |  | 78.8  | 162.1                           |  |  |   |

The first stage of each of the 12 thoracoplasties was performed within a few days of the end of the preparatory period of streptomycin therapy. The chemotherapy was continued in all patients until approximately two weeks after completion of the last stage. Each stage consisted of the resection of two ribs and all patients had supplementary anterior stages. An interval of three weeks elapsed between stages. The total course of streptomycin therapy in these 12 patients varied from 142 to 211 days, depending on the extent of the thoracoplasty and the length of the preparatory period.

There was no spread of disease in any patient during thoracoplasty. The decision to continue streptomycin therapy during the entire course of thoracoplasty was made because of the lack of any precedent in such cases. Because the first patients responded so favorably to this regimen, it has been continued to the present time. It is realized, however, that accumulating evidence in respect to resistance of tubercle bacilli to streptomycin may reveal that prolonged continuation of streptomycin therapy is illogical in many cases. No resistance studies were carried out on the organisms of any of these patients.

Streptomycin therapy was continued in the 3 patients with intrapleural pneumothoraces for an average of 49.6 days following induction of their pneumothoraces. Two of these patients had what appeared to be "tension" cavities which diminished considerably in size during the preparatory period of streptomycin therapy (cases 1 and 9). Pneumothorax was selected for these 3 patients in preference to thoracoplasty because of age or the presence of relatively extensive



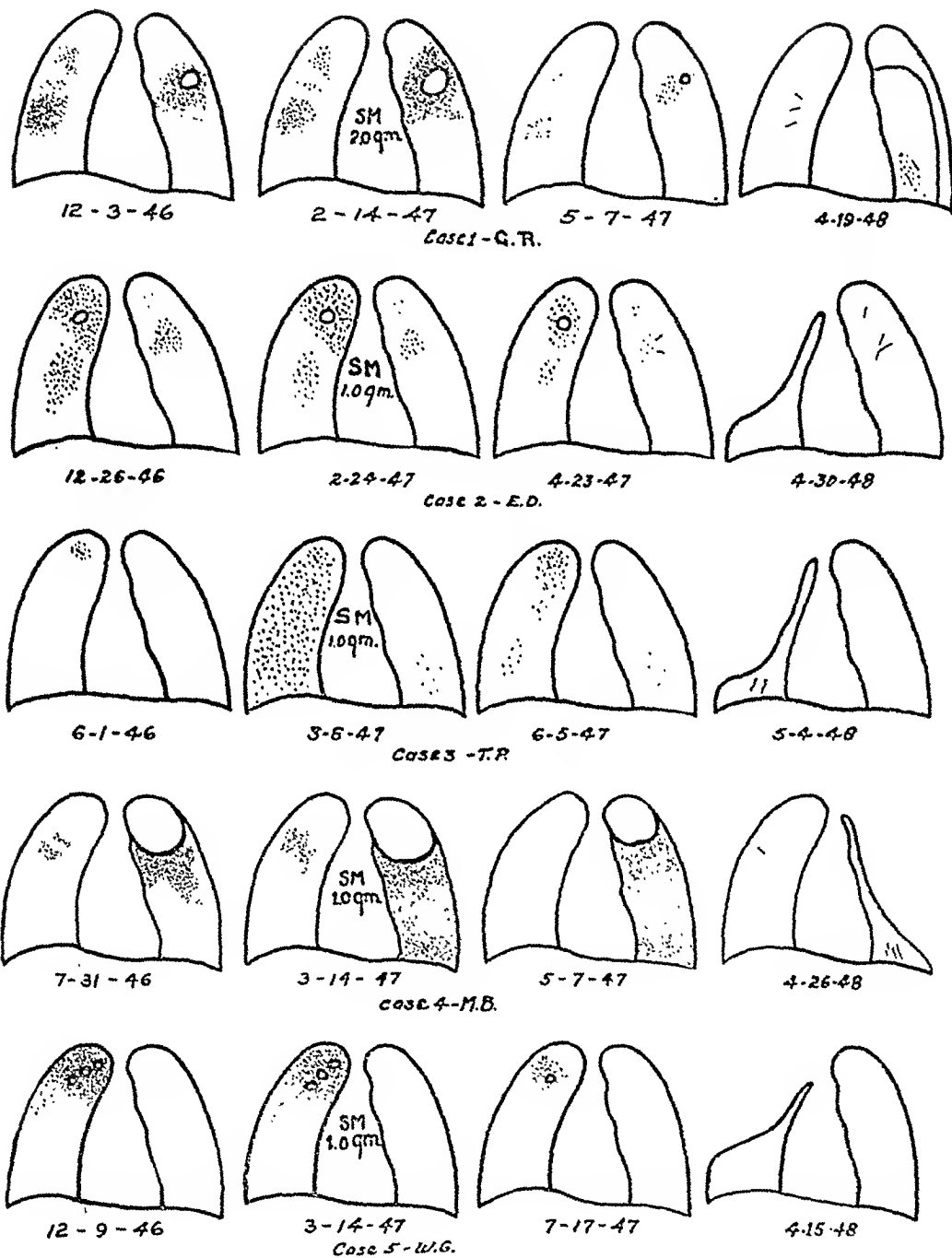


FIG. 1

FIGS. 1, 2, and 3. Diagrams illustrating roentgenological appearance of tuberculous lesions before, during and after streptomycin and collapse therapy. Predominantly exudative disease is indicated by the dotted areas; fibrotic lesions by lines; cavities by circles. The diagram representing the roentgenogram taken at the time of institution of streptomycin therapy is indicated together with the initial dose. The type of collapse therapy indicated may be identified, if necessary, by referring to table 1.

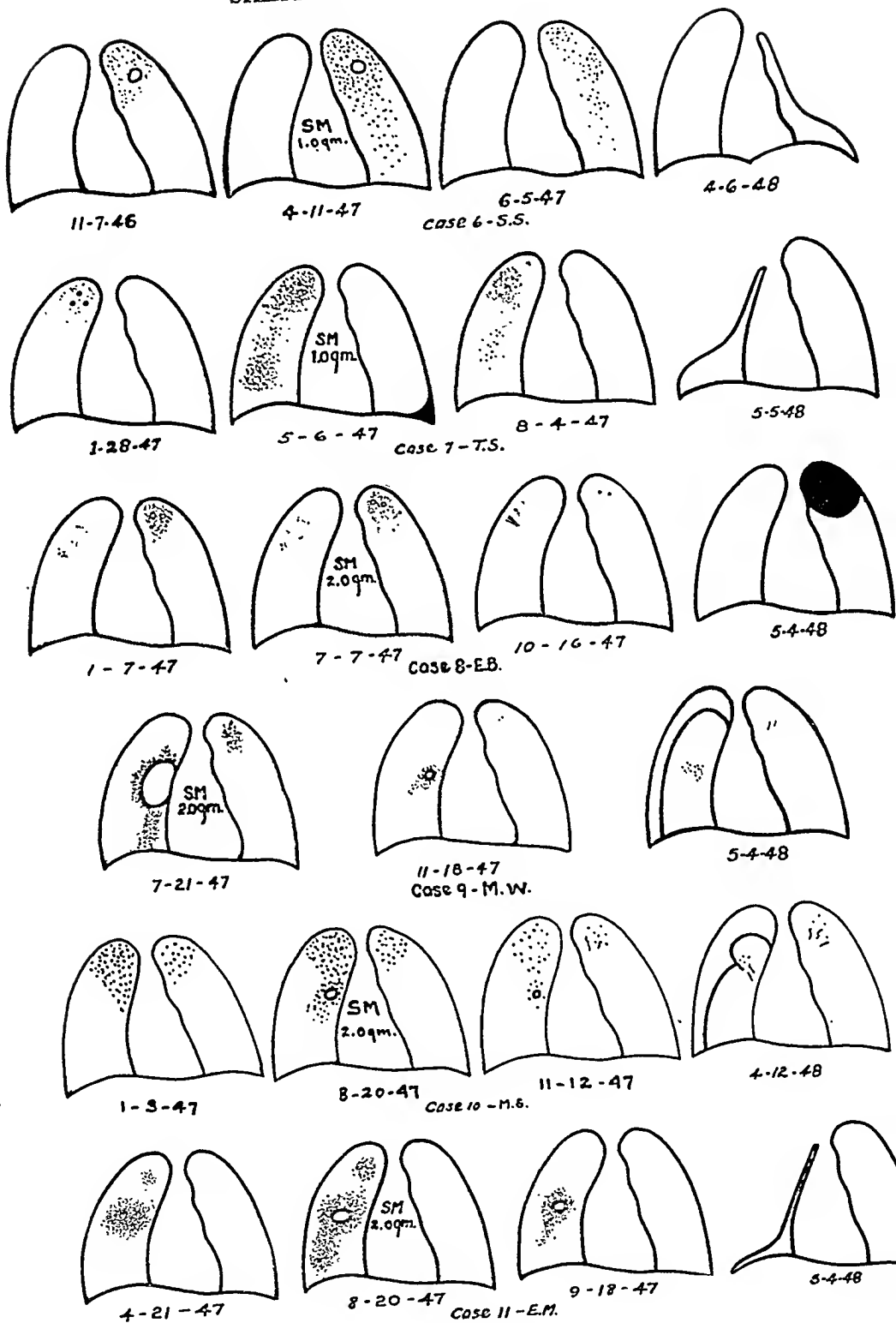
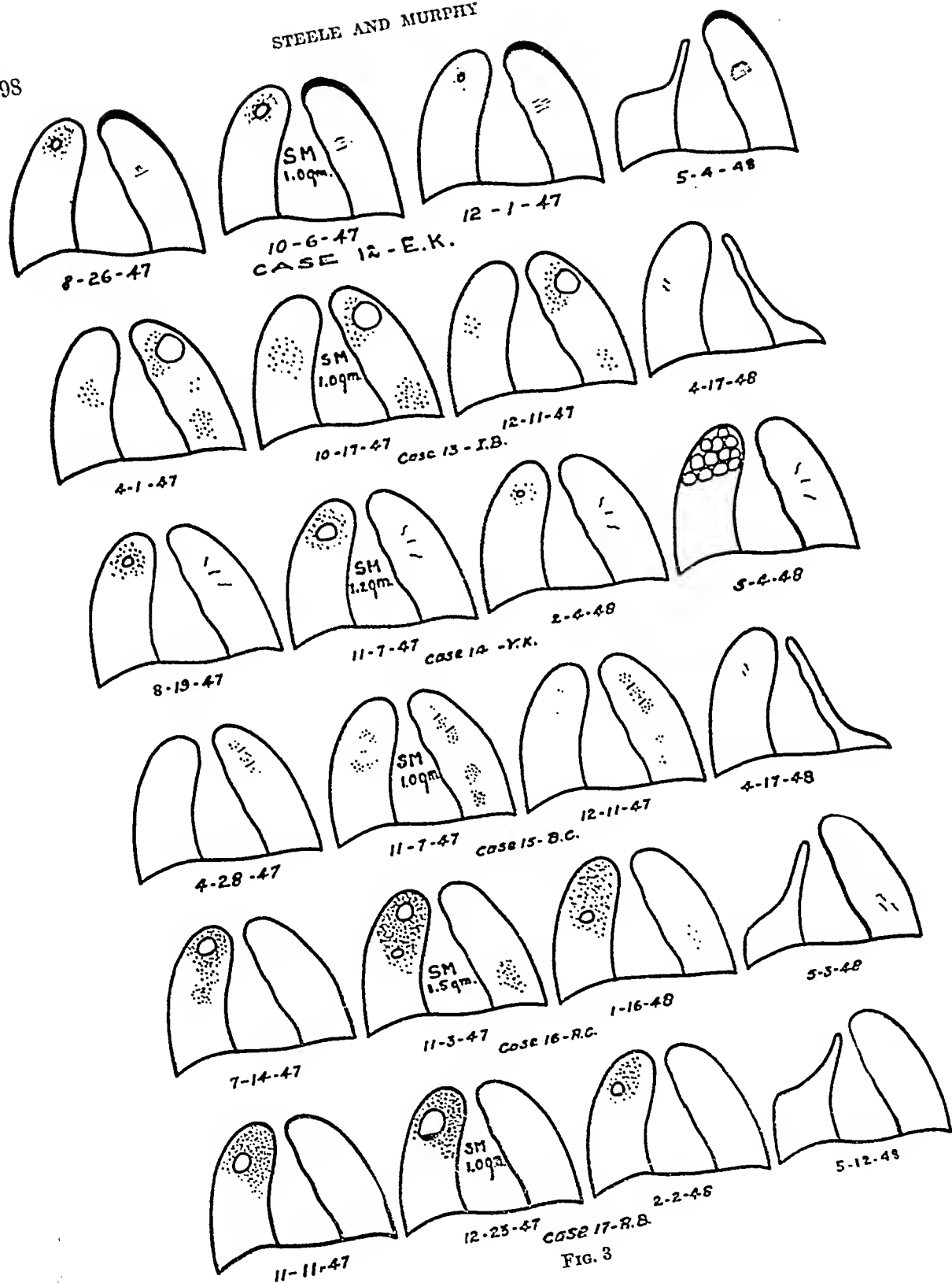


FIG. 2



contralateral lesions. In 2 of these 3 patients, intrapleural pneumonolyses were performed during the course of streptomycin therapy (cases 1 and 10).

Streptomycin therapy was continued for 17 days after the extrapleural pneumonolysis followed by paraffin filling (case 8). The operation was selected in this patient in preference to thoracoplasty because of her age and the rather limited extent of the lesion. The patient who had the extrapleural pneumonolysis followed by lucite ball filling (case 14) was the only one in the series in which the administration of streptomycin was discontinued after a preparatory period and reinstituted at the time of operation. Thoracoplasty had been recommended for this patient after 53 days of streptomycin therapy, but her husband refused to allow the operation to be performed and the extrapleural pneumonolysis was performed two months later as a substitute. Streptomycin was administered for 27 days following the operation.

The majority of the patients received 1.0 gm. of streptomycin daily. The dose in others ranged from 0.75 gm. daily to 2.0 gm. daily. One of the reasons for this variation was that a dosage schedule calculated according to weight was adopted in October 1947. The first patients in the series received the drug in five equally divided doses; this was later changed to three divided doses in twenty-four hours.

Three patients in the series had daily temperature elevations of from 100.2°F. to 103°F. prior to the institution of streptomycin therapy and the others all had low grade fevers. All responded favorably in this respect to streptomycin. Four patients gained considerable weight and 5 others showed a moderate weight gain during their preparatory periods; one patient lost slightly and the weight of the others remained stationary.

Prior to the institution of streptomycin therapy, the sputum of 14 patients contained tubercle bacilli revealed by direct smear or concentration. The sputum from the remaining 3 patients revealed tubercle bacilli on culture. Following the preparatory period and just prior to the institution of collapse therapy, the sputum of 1 patient was positive for tubercle bacilli on concentration; 7 had positive sputum cultures; 2 had positive cultures of their gastric contents; and the remaining 7 had negative cultures of sputum or gastric contents. The follow-up is too short to be of any significance in regard to the bacteriologic conversion of pulmonary secretions on completion of collapse therapy, or during a limited period thereafter. No tubercle bacilli were found, however, on culture of the pulmonary secretions of 13 patients after completion of their collapse therapy. It is realized that it is sometimes difficult to demonstrate tubercle bacilli in the pulmonary secretions of patients receiving streptomycin therapy.

The follow-up period is also too short to be of any significance in regard to relapses following therapy, as only 10 of the 17 patients have been followed for seven months to a year following collapse therapy. None, however, has had any progression of disease.

#### COMMENT

Streptomycin was used in this series of cases in preparing exudative lesions for collapse therapy. Without its use, most of the patients would never have been favorable candidates for collapse therapy and some, at least, would probably

have died from progression of their disease. Streptomycin not only prepared exudative lesions rapidly for collapse therapy, but also halted the progression of the disease in 13 of the 17 patients. It is estimated that the use of streptomycin in preparation for collapse therapy in this clinic has increased by at least 50 per cent the number of cases suitable for surgical collapse procedures.

#### SUMMARY

1. The use of streptomycin in 17 patients with predominantly exudative pulmonary tuberculosis in preparation for collapse therapy is reported. The disease of 13 of these patients was known to be progressive when streptomycin therapy was instituted.

2. The average preparatory period of streptomycin therapy was 78.8 days.

3. Twelve patients were prepared for thoracoplasty, 3 for intrapleural pneumothorax and 2 for extrapleural pneumonolysis.

4. In addition to the preparatory period, all patients received streptomycin during and after the institution of collapse therapy.

5. Streptomycin not only prepared the exudative lesions rapidly for collapse therapy, but also halted the progression of the disease in 13 of the 17 patients.

#### SUMARIO

##### *La Estreptomicina en la Preparación para la Colapsoterapia*

1. Descríbese el empleo de la estreptomicina como preparación para la colapsoterapia en 17 enfermos con tuberculosis pulmonar predominantemente exudativa. Al iniciar la estreptomicinoterapia, se sabía que la enfermedad en 13 de dichos enfermos era evolutiva.

2. La duración del período preparador de estreptomicinoterapia promedió 78.8 días.

3. Doce enfermos fueron preparados para la toracoplastia, 3 para neumotórax intrapleural y 2 para neumonolisis extrapleural.

4. Además del período de preparación, todos los enfermos recibieron estreptomicina durante la aplicación de la colapsoterapia y después.

5. La estreptomicina no sólo preparó las lesiones exudativas rápidamente para la colapsoterapia, sino que detuvo la agravación de la dolencia en 13 de los 17 enfermos.

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of severe cough, copious sputum, and marked toxemia, is first determined to have an adherent pleura by repeated needlings on the side of the chest having the cavity under consideration for Monaldi drainage. Then, under sterile surgical precautions and with the use of the fluoroscope, a needle is inserted into the cavity and pressure readings taken to determine the presence of a positive pressure cavity. If such a cavity is found to be present, a trocar is then inserted into the cavity and through the trocar a rubber catheter is introduced into the cavity and the trocar then withdrawn. The catheter is then secured to the chest wall by means of ligatures and adhesive plaster. Twenty-four hours later suction is begun. In the cases in this series the two-bottle method described by Kupka (3) was used. Suction is continuous, with the flow regulated so that the bottles require reversing every six hours.

#### COMPOSITION OF CLINICAL MATERIAL

The cases reviewed fell into two well-defined groups. In one group (23 patients) the procedure was not followed by a thoracoplasty, and in the other group (11 patients) the procedure was followed by a thoracoplasty in either one or two stages. In the first group the procedure was done for palliative reasons and hence that group may be called the "palliative group." The second group includes 4 patients on whom the procedure was performed for palliative reasons initially and who later improved to such an extent that a thoracoplasty could be performed. In addition, this group also contains 7 patients who were candidates for thoracoplasty but on whom thoracoplasty was deferred because of the presence of a positive pressure cavity. The second group may be titled the "pre-thoracoplasty group" as the Monaldi procedure was performed prior to, or as a preparation for, thoracoplasty.

*Distribution of cases:* The sex and age distribution of the patients studied and the group into which the patients fell are as follows. There were 21 men and 13 women patients. Four patients were in the age group 15 to 25, 11 patients in the age group 26 to 35, 9 patients in the age group 36 to 45, and 10 patients were over 45. In the palliative group, 3 patients were in age group 15 to 25, 7 in the group 26 to 35, 6 in the group 36 to 45, and 7 in the group over 45. In the prethoracoplasty group, 1 patient was in the age group 15 to 25, 4 in the group 26 to 35, 3 in the group 36 to 45, and 3 in the group over 45.

*Extent of tuberculous involvement:* Tuberculous involvement was relatively extensive in these patients. According to the National Tuberculosis Association Diagnostic Standards, 2 were in class 2B, 13 in class 3A, 10 in class 3B, and 9 in class 3C.

*Cavities:* Twenty of the cavities treated were on the right side of the chest while 15 were on the left side (one patient had a bilateral Monaldi). One cavity was in a lower lobe (right) while the remainder (34) were upper lobe cavities. The distribution of cavity pressure readings found at operation is illustrated by figure 1. It may be seen that the cavities for the most part registered a positive pressure. Pressure readings may have been higher had each cavity been carefully tested, with precautions taken to obtain an accurate reading. Lower pressure readings than actually exist may result unless special apparatus is used, namely, an adapter on the exploring needle with a two-way stopcock and connec-

# MONALDI CATHETERIZATION OF TUBERCULOUS CAVITIES<sup>1</sup>

A Review of 34 Cases

WM. A. WILBUR<sup>2,3</sup>

## INTRODUCTION

Historically, a direct approach to the treatment of pulmonary cavities dates back to 1845 when Hastings and Starks introduced a rubber catheter into a large apical cavity, apparently with improvement in the patient's condition. A most important step in the understanding of cavity mechanism came in 1936, when Coryllos (1) by gas analysis proved the degree of patency of a draining bronchus. Monaldi, an Italian physician, was convinced that mechanical causes were the principal factor in the causation and persistence of giant cavities and he began treating such cases in the spring of 1938 by means of suction drainage in an attempt to neutralize the mechanical factors. He reported on his first cases (2), treated with the procedure which now bears his name, in June 1938. Kupka and Wells (3) described Monaldi's technique in 1940 and later that year Kupka and Bennett (4) reported on a series of cases undergoing Monaldi drainage. Vineberg and Kunstler (5) in 1944 contributed an excellent paper on the treatment of pressure cavities. They noted that of 119 postthoracoplasty cases 12 had persistent cavities, and these, upon needling, were found to be "tension" or positive pressure cavities. They strongly believe that any cavity over 2.5 cm. should be investigated before doing a thoracoplasty and, if a tension cavity is found, Monaldi catheterization is advocated as a preliminary to thoracoplasty.

Theoretically, Monaldi catheterization appears to be a direct approach to an important problem in the field of tuberculosis. Relatively few articles have appeared on this subject in American periodicals. Because of the newness of the procedure and the scarcity of reports on its use, it was believed that a review of the cases treated in Alameda County Hospitals might add further knowledge as to its value. Each of the 34 cases included in this report is a "completed" case, insofar as hospital records go, in that the patient was either discharged, released against advice, or died in the hospital. The period covered in this report extends from January 1940 to January 1947.

## TECHNIQUE

The technique of the operation has been described by others (3, 5) and the details will not be repeated here. In general, a similar procedure was followed in this series of cases. For example, a patient suspected of having a partially blocked or "positive pressure" cavity from roentgenographic findings of a balloon-type cavity, or from the presence

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of severe cough, copious sputum, and marked toxemia, is first determined to have an adherent pleura by repeated needlings on the side of the chest having the cavity under consideration for Monaldi drainage. Then, under sterile surgical precautions and with the use of the fluoroscope, a needle is inserted into the cavity and pressure readings taken to determine the presence of a positive pressure cavity. If such a cavity is found to be present, a trocar is then inserted into the cavity and through the trocar a rubber catheter is introduced into the cavity and the trocar then withdrawn. The catheter is then secured to the chest wall by means of ligatures and adhesive plaster. Twenty-four hours later suction is begun. In the cases in this series the two-bottle method described by Kupka (3) was used. Suction is continuous, with the flow regulated so that the bottles require reversing every six hours.

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*Distribution of cases:* The sex and age distribution of the patients studied and the group into which the patients fell are as follows. There were 21 men and 13 women patients. Four patients were in the age group 15 to 25, 11 patients in the age group 26 to 35, 9 patients in the age group 36 to 45, and 10 patients were over 45. In the palliative group, 3 patients were in age group 15 to 25, 7 in the group 26 to 35, 6 in the group 36 to 45, and 7 in the group over 45. In the prethoracoplasty group, 1 patient was in the age group 15 to 25, 4 in the group 26 to 35, 3 in the group 36 to 45, and 3 in the group over 45.

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tions made to a manometer so that pressure readings may be taken without allowing air to escape. Such apparatus was not used routinely in this series of cases as far as can be determined. Suction was continued for an average of 13.7 months (range 0.5 to 33 months) in the palliative Monaldi group, as compared with 10.5 months (range 3 to 23 months) in the prethoracoplasty Monaldi group.

Cavity size was studied. Chest films were selected so that the initial cavity size measurement was the measurement found on the roentgenograms obtained just prior to the start of Monaldi drainage. The final cavity size was determined by the last chest film available on each patient. As only posterior-anterior films were taken, the measurements are in terms of the greater and the lesser diameter of the cavities found.

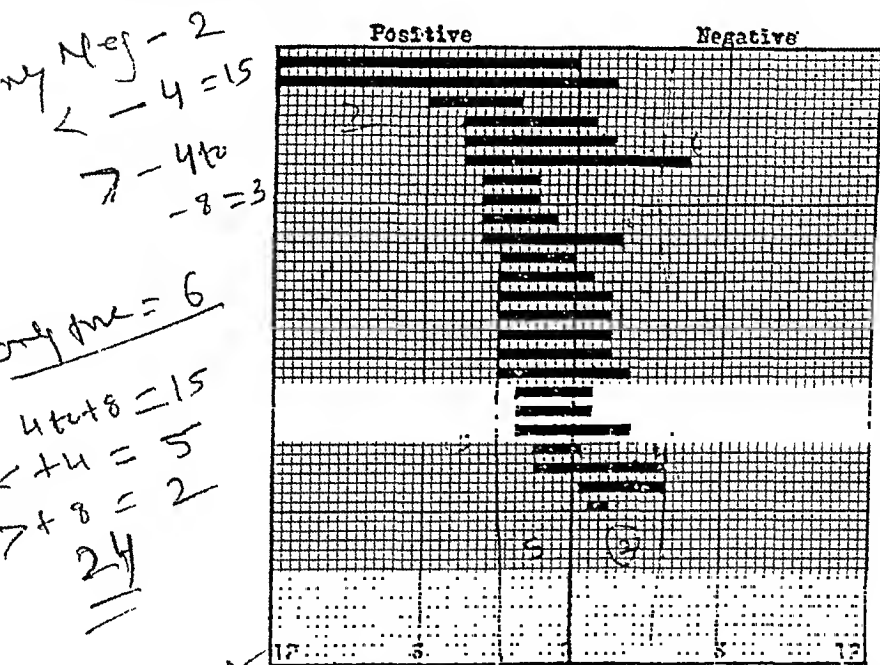


FIG. 1. Maximum and minimum pressures in 24 cavities. Pressure in centimeters of water.

#### RESULTS

$$15 + 4 = 6$$

$$3 - 74$$

**Cavity closure:** In reviewing the group of patients in the prethoracoplasty group, it was necessary to form three subgroups according to the data available. The first such subgroup consists of 5 patients with complete roentgenographic studies and on whom cavity pressure measurements were recorded. Initially, the greater diameter of the cavities ranged from 5 to 7 cm. and the lesser diameter from 3 to 6 cm. The average cavity reading in centimeters of water was plus 3.6 (inspiration) and minus 1.4 (expiration); with a range of plus 5 to plus 2 on inspiration and of plus 2 to minus 5 on expiration. The result in 3 of these patients was a closed cavity for a minimum of 20 weeks in one patient, 100 weeks in another and 110 weeks in the third. Cavity closure was determined from follow-up chest films and the time of its occurrence was calculated from the end of Monaldi

drainage. In one patient an area of rarefaction remained (without change for a period of 240 weeks) on the chest roentgenograms following Monaldi drainage, but the patient's sputum became negative for tubercle bacilli. In the absence of proper roentgenographic studies, this cavity is considered to be "questionably closed." In the fifth patient the cavity remained open though reduced in size from 6 by 4 cm. to 2 by 2 cm. This patient developed an empyema following her first stage thoracoplasty and the second stage could not be performed.

The next subgroup is composed of 3 patients on whom chest roentgenographic studies were complete, but on whom a measurement of cavity pressure at time of operation was not recorded. The greater diameter of these cavities ranged from 4 to 6 cm. and the lesser diameter from 3 to 4 cm. The result in all 3 patients was a closed cavity for a minimum of 100 weeks in one patient, 127 weeks in another, and 161 weeks in the third, as shown by follow-up chest films.

The third subgroup also contains 3 patients. In the case of these patients the chest roentgenograms had been either lost or destroyed. On examination of the clinical records which contained diagrams of chest plates, it was noted that in one patient the initial cavity size was 7.5 by 4.5 cm., and in another it was 6 by 5 cm. No cavity pressure readings were recorded on these 2 patients. In the third patient no definite cavity size measurement was recorded, but a cavity pressure reading was given as plus 4 to minus 2 cm. of water. The result in 2 patients was a closed cavity, while in the third patient the cavity reopened following a one-stage thoracoplasty.

To summarize the prethoracoplasty group, in 9 patients a closed cavity was obtained (including one questionable case), while in 2 patients the cavity remained open. In the 2 patients who failed to achieve a closed cavity, only a one-stage thoracoplasty had been performed.

The palliative group is also divided into 3 subgroups according to the data available. In the first subgroup there are 7 patients. Initially, in these patients the greater diameter of the cavities ranged from 5 to 9 cm. and the lesser diameter from 3 to 7 cm. Cavity pressure readings at time of operation averaged plus 4.4 and minus 1.4 cm. of water with a range of plus 3 to plus 6 cm. (inspiration) and plus 2 to minus 6 cm. (expiration). All cavities in this subgroup were reduced in size. Final cavity size measurements showed a greater diameter range of 1 to 5 cm. and a lesser diameter of 1 to 2.5 cm.

In the second subgroup there are 3 patients. Chest roentgenograms were available for review but cavity pressure readings had not been recorded. Initial cavity size measurements showed a greater diameter range of 5 to 9 cm. and a lesser diameter range of 4 to 6 cm. All cavities in this subgroup were reduced in size. Final cavity size showed a greater diameter range of 2 to 3 cm. and a lesser diameter range of 1 to 3 cm.

In the third subgroup there are 13 patients on whom the data are incomplete. On 3 patients the initial cavity size could be determined (8 by 6 cm., 7 by 3 cm., and 10 by 5 cm., respectively). Follow-up studies revealed that 2 of these patients died; one in two weeks, and one in ten weeks. The third patient went home, greatly improved, with Monaldi drainage in use six weeks after it had been

initiated. In 10 patients no definite measurement of cavity size was noted in the clinical records, but the cavities were considered clinically to be of the positive pressure type. Cavity pressure readings were as follows: plus 12 to 0; plus 8, plus 3; plus 6, minus 1; plus 6, minus 2; plus 3, minus 1; plus 2, minus  $\frac{1}{2}$ ; minus  $\frac{1}{2}$ , minus 2; and minus 1, minus 2. In 2 patients no cavity pressure reading had been recorded. Results in these 10 patients showed reduction in cavity size in 5 patients and no change in cavity size in 4 patients. In one patient there was no record as death occurred three months after start of Monaldi drainage.

To summarize the results in 23 patients in the palliative group, 15 cavities were reduced in size and 8 cavities either showed no change or the records were incomplete as to the result obtained.

*Sputum:* Analysis of sputum records revealed that 26 patients continued to have sputum positive for tubercle bacilli. Twenty-two were in the palliative group and 4 were in the prethoracoplasty group. Eight patients are considered to have converted their sputum to "negative." Seven of these patients were in the prethoracoplasty group and one patient was in the palliative group. There was a great variation in the time it took for the sputum to become negative for tubercle bacilli. The range was from two months after starting Monaldi drainage in one patient up to two years and six months in another patient. Two patients converted their sputum to "negative" before undergoing thoracoplasty. In 5 patients in the prethoracoplasty group, whose sputum became negative for tubercle bacilli as determined by cultures, the average length of time taken to "convert" their sputum was 16.3 months from the start of Monaldi, and 8.5 months from the start of thoracoplasty or end of Monaldi. In table 1 may be seen the relationship between thoracoplasty, duration of Monaldi drainage, and the time required for sputum to become "negative" in the 8 patients considered to have done so in this series. The patient in the palliative group whose sputum was negative for tubercle bacilli continued to be noninfectious for nine months, at which time he was discharged with Monaldi drainage still in use. Two patients in the prethoracoplasty group closed their cavities but still had tubercle bacilli in their gastric lavages and the 2 patients in this group who did not close their cavity continued to discharge tubercle bacilli in the sputum.

*Clinical course:* An attempt was made to answer the question as to whether or not Monaldi drainage was effective in bettering the survival time of the patients treated. The answer must be given in terms of probability, for a control group does not exist and survival time may not indicate the effect of treatment. In addition, more than one factor enters into each case and the presence of so many variables makes the assessment of any one factor difficult, if not impossible. Evaluation was made on the basis of progress notes, nursing notes, clinical course, and the estimation of the physicians who were treating these patients. These four sources were found to be in agreement in all except one patient in which there was a difference of opinion in the estimation given by physicians.

In the 18 patients who died in the palliative group, the average length of survival calculated from the start of the procedure was found to be sixteen months; the minimum was two weeks and the maximum was thirty-three months. In the

7 patients in this group who were considered to have benefited from the procedure, the average length of survival was twenty-nine months, and in the 11 patients considered *not* to have been benefited it was seven and one-half months. It is important to note that of the 19 deaths in this series, 18 were in the palliative group. Six of these patients were classified as 3B (National Tuberculosis Asso-

TABLE 1

*The relationship of the bacteriologic status of the sputum to thoracoplasty and to duration of Monaldi drainage*

| CASE NUMBER | SPUTUM RESULT (POSITIVE OR NEGATIVE FOR TUBERCLE BACILLI) | THORACOPLASTY STAGES (1 OR 2) | DURATION OF MONALDI | ELAPSED TIME FOR SPUTUM TO BECOME "NEGATIVE" |  | LENGTH OF "NEGATIVE" SPUTUM FOLLOW-UP | SPUTUM "NEGATIVE" TO CULTURE |
|-------------|---|-------------------------------|---------------------|--|--|---------------------------------------|------------------------------|
|             |   |                               |                     | From start of Monaldi                        | From end of Monaldi and start of thoracoplasty |                                       |                              |
|             |   |                               | months              | months                                       | months   | months                                |                              |
| 1           | Negative  | 2                             | 5                   | 30   | 25   | 6                                     | Yes                          |
| 2           | Negative  | 2                             | 17                  | 27.5   | 10.5   | 9                                     | Yes                          |
| 3           | Negative  | 1                             | 7                   | 11   | 4  | 7                                     | Yes                          |
| 4           | Negative  | 2                             | 8                   | 11   | 3  | 1 week                                | Yes                          |
| 5           | Negative  | 1                             | 3                   | 2  | *  | 45                                    | Yes                          |
| 6           | Negative  | 1                             | 16                  | 2  | *  | 10 <sup>1</sup>                       | Not cultured <sup>2</sup>    |
| 7           | Negative  | 1                             | 10                  | 14   | 4  | Neg. on disc.<br>No follow-up         | Not cultured                 |
| 8           | Positive <sup>3</sup>                                     | 2                             | 5                   | —  | —  | —                                     | —                            |
| 9           | Positive <sup>3</sup>                                     | 1                             | 5                   | —  | —  | —                                     | —                            |
| 10          | Positive <sup>4</sup>                                     | 1                             | 23                  | —  | —  | —                                     | —                            |
| 11          | Positive <sup>4</sup>                                     | 1                             | 16                  | —  | —  | —                                     | —                            |
| 12**        | Negative  | Not done                      | More than 17        | 7  | Monaldi in use on disc.                        | 9                                     | Not cultured <sup>2</sup>    |

<sup>1</sup> No sputum on discharge but sinus tract drainage persisted and contained tubercle bacilli. Patient's private physician reports this sinus eventually closed, but date not known.

<sup>2</sup> "Negative" to 1 week sputum concentration.

<sup>3</sup> Gastric lavage contains tubercle bacilli.

<sup>4</sup> Cavity remained open following thoracoplasty.

\* Sputum became "negative" prior to thoracoplasty.

\*\* Palliative group patient (all others are in prethoracoplasty group).

ciation Diagnostic Standards) and 8 as 3C, and, as the term palliative implies; there was little hope of doing more for them than giving them relief of symptoms.

An attempt has been made to evaluate the available evidence to show whether or not the patient was made more comfortable as a result of Monaldi drainage. Evidence of comfort to the patient included less cough, less sputum, decreased toxemia, gain in weight and improvement in general appearance. Twenty-five

of the 34 patients received symptomatic relief and in 9 patients no apparent improvement was noted. Three of the patients in the palliative group who were aided by the procedure showed striking improvement with the cessation of excessive cough and expectoration resulting from a well-functioning Monaldi drainage. Of 23 patients in the palliative group, 15 received symptomatic relief and 8 received no apparent relief.

*Concurrent therapy:* The most common concurrent therapy was the use of pneumoperitoneum in 14 patients. Homolateral phrenic nerve crush had been done on 6 patients at various times. Four were done prior to starting Monaldi drainage (6 years, 5 months, 21 months, 7 months, and 4 months, respectively), and two were done while Monaldi drainage was in use. Five of these 6 patients also had pneumoperitoneum. Bronchoscopy was done on three occasions in one patient and on one occasion in 4 patients during Monaldi drainage. Proper evaluation of concurrent therapy is not possible, but pneumoperitoneum, phrenic nerve crush, and bronchoscopy are believed to have been of positive benefit.

Of the 11 patients in the prethoracoplasty group, 7 had a one-stage thoracoplasty and 4 had a two-stage thoracoplasty. In 9 cases, anterior rib resection was done to avoid contamination of the thoracoplasty wound, for at operation the Monaldi sinus tract may accidentally be entered. In 5 of these cases it was done four to six weeks prior to thoracoplasty. In one patient it was done one month prior to Monaldi drainage. In the remaining 3 patients the anterior rib resection was done in anticipation of a thoracoplasty, but, presumably because the patient's general condition did not permit it, thoracoplasty was not done.

One patient who was in the palliative group, and who ultimately died without apparent benefit from the procedure, had Monaldi drainage of a cavity in the lower lobe of the right lung. All other cavities treated were in the upper lobes of the lung. In one patient Monaldi catheterization was done on both sides of the chest. Drainage was started on the left side in November 1941 and on the right side in June 1943, and was continued on both sides until the patient died in July 1944.

*Complications:* Secondary infection of the Monaldi sinus was present in all of the 34 cases. It proved to be of little consequence except that repeated dressings were required to combat the malodorous drainage around the catheter. The next most common complication was hemorrhage through or around the catheter, and this occurred in 5 patients. Four patients developed a bronchopleural-cutaneous fistula at the site of and following removal of the Monaldi catheter. In one patient the fistula followed an empyema which in turn followed thoracoplasty. The thoracoplasty had not been preceded by an anterior rib resection, and in spite of the fistula the cavity closed. Two other patients in the prethoracoplasty group also developed a bronchopleural-cutaneous fistula. In one of these, cavity closure occurred while in the other the cavity did not close. One patient in the palliative group developed a bronchopleural-cutaneous fistula which remained open until the patient died. One patient developed empyema following thoracoplasty in spite of preliminary rib resection, and a planned second-stage operation was not done. Two patients had persistent sinus tracts which drained for

four years and five months in one case, and for four years and six months in the other before finally healing.

*Deaths:* Nineteen of the 34 patients died in the hospital. The degree of infection present has already been indicated with 32 of the 34 patients being considered to have "far advanced" tuberculosis. In 23 patients the procedure was done for palliative reasons and 18 of the 19 deaths were in this group. Causes of death were as follows: (a) pulmonary hemorrhage, 3 patients, in one instance through the Monaldi tube; (b) cardiovascular disease, 3 patients (cor pulmonale, syphilitic heart disease, and congestive heart failure, respectively); (c) tuberculous meningitis, 2 patients; (d) spontaneous pneumothorax on the side of the chest opposite the Monaldi drainage, one patient; and (e) overwhelming pulmonary tuberculosis, 10 patients. One of the deaths from meningitis was of the patient with bilateral Monaldi drainage and occurred thirty-three months after drainage had been started on the left side and thirteen months after drainage had been started on the right side. Drainage of both sides was functioning at time of death. The other death from meningitis occurred sixteen months after start of Monaldi drainage.

#### COMMENT

There are certain disadvantages and dangers to the Monaldi procedure, exclusive of the surgical risk. Some of these have already been mentioned under complications. Hemorrhage may occur regardless of the presence of Monaldi suction, yet it must be considered as a danger. Secondary infection with accompanying malodorous discharge, extrusion of catheters which require replacement, persistent draining sinus tracts, and the formation of a bronchopleural-cutaneous fistula, although not dangers, are certainly disadvantages. Empyema, although it should not develop in a properly selected and treated case, is a possible complication and a dangerous one. An important disadvantage with the present scarcity of trained nursing personnel is the increased nursing care which is demanded, especially in the early months of treatment. Dressings must be changed, suction bottles regulated to maintain suction, and accessory drainage tubes require cleaning. The maintenance of adequate suction is of primary importance to the success of the procedure, and the presence of adequate nursing personnel is, therefore, a most necessary requirement.

The present series of 34 patients who received Monaldi drainage fell into two groups. In one group the procedure was carried out for palliative reasons only, *i.e.*, because of the severe cough, toxemia, and copious sputum associated with the presence of a positive pressure cavity. The other group was designated as the prethoracoplasty group and included those patients who, following Monaldi drainage, underwent a thoracoplasty. This group includes 4 patients who, although initially treated for palliative reasons, later improved to such an extent that a thoracoplasty could be performed, and also those patients who were candidates for thoracoplasty but on whom thoracoplasty was not considered advisable in the presence of a positive pressure or "balloon type" cavity. In these patients Monaldi drainage was done as a preliminary to thoracoplasty.

Eight patients out of 11 in the prethoracoplasty group closed their cavities, while in one there was questionable closure (with "negative" sputum) and in two cases the cavity remained open. None of the patients in the palliative group obtained cavity closure, but in 10 patients out of 23 on whom measurements were possible there was a significant reduction in cavity size. Eight patients were considered to have converted their sputum to "negative" and 7 of them were in the prethoracoplasty group. One patient in the palliative group had sputum negative for tubercle bacilli for at least nine months. Four prethoracoplasty patients did not convert their sputum. Two of these patients had closed their cavities while 2 had not. Twenty-two of the 23 palliative group patients continued to have sputum positive for tubercle bacilli.

In those patients who died and on whom a measurement of survival time was possible, it was found that 7 patients may have been benefited while 11 patients apparently were not benefited. The average survival period was twenty-nine months in those with benefit in contrast to seven and one-half months in those without benefit. In the palliative group 15 patients received relief while in 8 patients there was no apparent relief from symptoms.

Patients who are to have a thoracoplasty probably should have a preliminary anterior rib resection to avoid contamination at surgery for thoracoplasty. Secondary infection of the Monaldi tract, persistent sinus drainage of long duration, and formation of a bronchopleuro-cutaneous fistula are minor complications of the procedure, while pulmonary hemorrhage and empyema are major complications.

The question as to whether Monaldi is a worthwhile procedure presents itself. From the viewpoint of its complications, dangers, and disadvantages, it is obviously a procedure requiring careful consideration and judgment before it is to be used. As a palliative procedure in a patient with severe toxemia, there would appear to be little to lose and much to gain for increased survival time may result and symptomatic relief may be obtained as a minimum result. In patients with a tension cavity who are not severely toxic, yet are obviously not candidates for thoracoplasty, the use of Monaldi drainage, in addition to routine sanatorium care, may result in improvement to the point that a successful thoracoplasty can be done. In general, patients with tension cavities do not respond well to thoracoplasty and Monaldi drainage would appear to be a worthwhile procedure prior to thoracoplasty in such cases. Of 11 patients in the prethoracoplasty group, the cavity failed to close in 2 after thoracoplasty. In each of these a single-stage thoracoplasty was done and it was presumably inadequate.

#### SUMMARY

1. Thirty-four clinical records of patients who received Monaldi drainage for tuberculous cavities have been reviewed and analyzed. The cases fell into two groups. In one group the procedure was carried out for palliative reasons only, whereas the other group was able to have subsequent thoracoplasty.

2. Nine out of 11 patients having thoracoplasty following Monaldi drainage obtained cavity closure (including one "questionably closed" cavity with sputum

negative for tubercle bacilli). None of the 23 patients in the palliative group obtained cavity closure.

3. Seven patients in the prethoracoplasty group became sputum "negative" while 4 failed to do so. One patient in the palliative group became sputum "negative" while 22 remained infectious.

4. Symptomatic relief was obtained in 15 out of the 23 patients in the palliative group.

5. Monaldi drainage of positive pressure tuberculous cavities should be done in two general types of patients. It may be used purely as a palliative procedure or it may be used as a preparation for thoracoplasty, principally in patients with "tension" cavities.

#### SUMARIO

##### *La Aspiración de Monaldi en las Cavernas Tuberculosas*

1. Repásanse y analizan 34 protocolos clínicos de enfermos en quienes se efectuó el sondaje de Monaldi por cavernas tuberculosas. Los casos corresponden a dos grupos. En uno se realizó el procedimiento puramente por razones paliativas, en tanto que el otro grupo quedó en aptitud para la toracoplastia después.

2. En 9 de 11 enfermos en que se ejecutó la toracoplastia consecutivamente a la canalización de Monaldi se obtuvo cierre de la caverna (comprendiendo una caverna "dudosamente cerrada" con esputo negativo para bacilos tuberculosos). En ninguno de los 23 enfermos del grupo paliativo obtúvose cierre de la caverna.

3. En 7 enfermos del grupo pretoracoplástico el esputo se volvió "negativo", en tanto que en 4 no sucedió esto. En un enfermo del grupo paliativo el esputo se volvió "negativo," mientras que 22 continuaron infecciosos.

4. En 15 de los 23 enfermos del grupo paliativo se obtuvo alivio sintomático.

5. El sondaje de Monaldi para las cavernas tuberculosas de presión positiva debe ejecutarse en dos clases generales de enfermos: ya puramente como procedimiento paliativo o como preparación para la toracoplastia, principalmente en los casos con cavernas infladas.

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# BRONCHOSCOPY IN PULMONARY TUBERCULOSIS<sup>1</sup>

## A Study of Post-bronchoscopic Increase of Disease

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### INTRODUCTION

Ever since the first use of bronchoscopy in patients with pulmonary tuberculosis there have been misgivings in the minds of both patients and physicians regarding the possibility of aggravation of the disease by the procedure. The literature contains few data on the relative safety or danger of this type of examination in patients. Chevalier Jackson, in 1922 and 1927, stated that "the bronchoscopic study of tuberculosis is very interesting, but only a few cases justify bronchoscopy" (1). As early as 1931 Clerf (2) reported the examination of a large group of tuberculous patients among whom "no ill effects were noted from the bronchoscopy itself." No details of his observations were given. Myerson (3, 4), one of the pioneers in the field, reported in 1934 that no increases or reactivations of the pulmonary disease had occurred in his series of 150 patients, in all of whom the lesion was thought to be quiescent. He warned, however, that in his opinion no patient with an acute lesion should be bronchoscoped. Ten years later (5), he reiterates his belief that patients for bronchoscopy must be carefully selected and concludes that, because of the danger of reactivating the disease, only patients in whom it is relatively inactive should be subjected to the procedure. It is not entirely clear, however, whether he is referring to parenchymal or endobronchial disease. In 1939, McIndoe and his group (6) reported a series of single bronchoscopies in 272 patients with pulmonary tuberculosis, four of whom showed an increase of the disease which occurred shortly after the operation. They felt this to be no more than might be expected on a coincidental basis. Hawkins (7), the same year, observed one patient in whom the disease spread and an additional 3 patients who died within three weeks following bronchoscopy out of a total of 516 such examinations. He concluded in retrospect that each of these 4 patients had been too sick to undergo the procedure. Other isolated cases of postbronchoscopic pulmonary reactions have been mentioned by Amberson, as quoted by Jenks (8), Warren and co-workers (9), and Packard and Davison (10), all of whom believed the increase of disease to be the result of bronchoscopy. In 1943, a study bearing directly on the problem was published by Radner (11). He analyzed 183 bronchoscopies done over a one year period in 97 patients. Five of these patients developed atelectasis of a lobe or lung and 21 showed minimal infiltrative increases of the disease in the third to fifth week after bronchoscopy. In this series, all those who had shown progression of the disease prior to bronchoscopy (how long prior not stated) were excluded.

The present study was undertaken primarily to determine the statistical frequency of increase of disease following bronchoscopy in patients with active

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pulmonary tuberculosis and, secondarily, to investigate certain aspects of those cases in which it occurred.

#### MATERIALS AND METHODS

The present survey includes all the bronchoscopies done on patients with pulmonary tuberculosis in Trudeau Sanatorium during the ten year period from October 1936 to October 1946, comprising a total of 473 bronchoscopies in 233 patients.

Virtually all of the 233 patients in the series had tubercle bacilli in their sputum sometime during their residence in the Sanatorium, and the great majority were infectious at the time of bronchoscopy. All patients had stereoscopic roentgenograms of the chest made at least every six weeks and sometimes more often. The reports of the roentgenograms, as interpreted by the resident radiologist, were obtained from the clinical records and were the sole basis for determining whether or not there had been an increase of disease. From a roentgenographic standpoint, increase of disease was manifested by the appearance of new shadows within the lung or by a definite increase in the size of those shadows already present. These changes were interpreted as the development of *infiltration* or *reaction*, and were the only findings regarded in this study as *increase of disease*. Thus, reports of enlargement of cavities or of the development of pleural fluid were excluded, as were those in which the findings were questionable or ambiguous<sup>3</sup>.

In order to assess the factor of coincidental progression of the disease properly, an attempt was made to survey each patient for a six month period of time both before and after bronchoscopy. This total observation period of one year was divided into sections of two months each, using bronchoscopy as the central point. By this means, a comparison could be made of the incidence of increases in each two month section of the patient's course during the period of observation. The majority of patients were observed for the full twelve month period, although some could be surveyed only for a considerably shorter time. Selection of a two month interval in which to determine incidence of increases was an arbitrary matter, dictated chiefly by the possibility that development of tuberculous reaction or new disease within this period of time following bronchoscopy might well be a consequence of the procedure.

A representative sample of the method of charting is illustrated in figure 1. The point at which bronchoscopy was carried out is signified by the vertical line in the center of the chart; and the length of time each patient was observed, by the horizontal blocks divided into sections of two months each. The two month section immediately following bronchoscopy is designated by crosshatched blocks. Increases are shown by the small arrows. Those which occurred within less than one month of each other were grouped together and marked on the chart as only one increase. In the case of patients who were bronchoscoped more than once, there was often overlapping of pre- and postbronchoscopic observation time. Thus, frequently the six month survey period after one bronchoscopy

<sup>3</sup> For the sake of brevity, the term "increase" hereafter will refer to roentgenographic evidence of extension of the process, as defined above.

corresponded in whole or in part to the six month period before the next one. In such a situation, the reduplicated time is shown on the chart by a block marked in interrupted lines prior to the second of the two bronchoscopies.

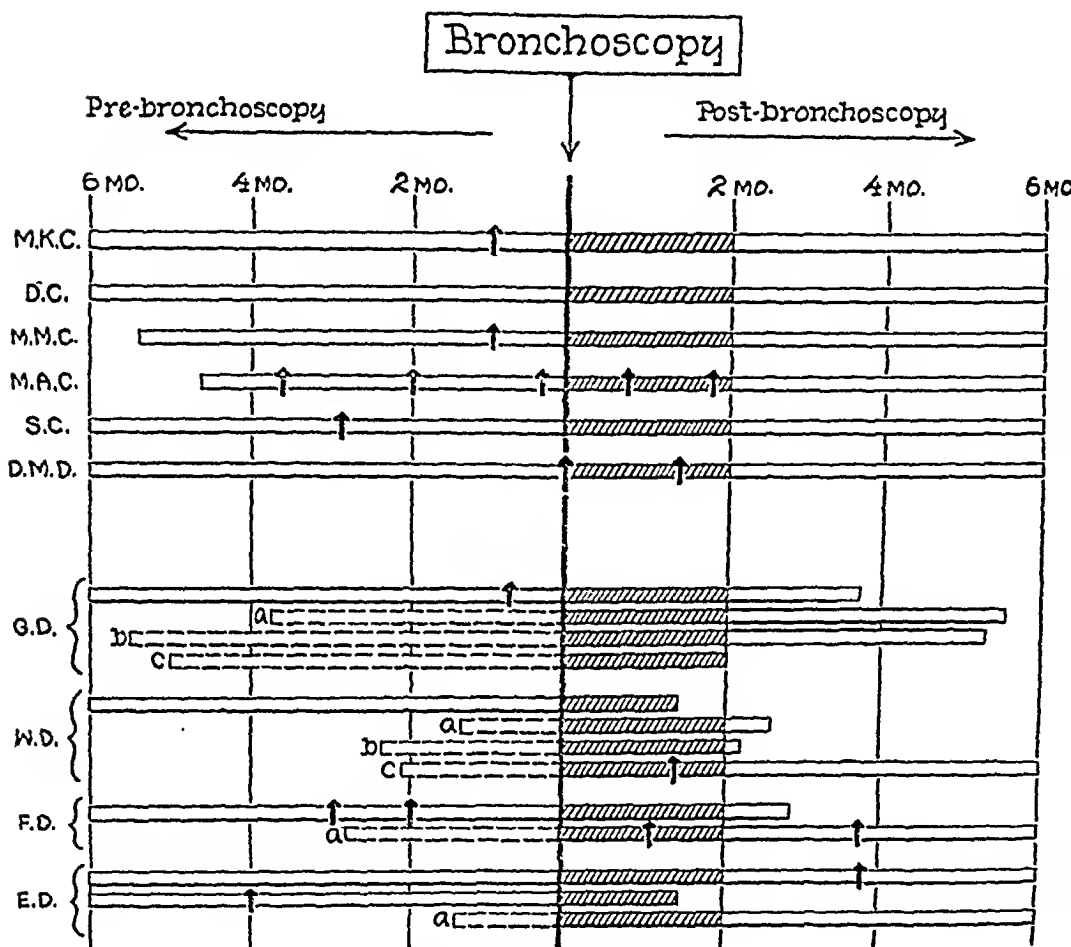


FIG. 1. Sample of survey method

↑ = roentgen evidence of increase of disease.

In the group with more than one bronchoscopy: a, b, c = reduplication of time block following previous bronchoscopy, covering elapsed time between bronchoscopies.

## RESULTS

Tabulation of the results revealed that 73 (15.4 per cent) of 473 bronchoscopies were followed within two months by roentgenographic evidence of increase of disease. This occurred in 59 (25.6 per cent) of the total of 233 patients.

In table 1 are shown the figures used for determination of the incidence of increases in each two month section of the one year observation period. The data are analyzed in terms of patient-months of observation, and total number of increases in two months' time. In a given section, both the total months of

TABLE 1

*Incidence of roentgenographic increase of disease in three groups for 6 two month sections*

Two month sections correspond to those shown in figure 1. Incidence of increase of disease equals total number of increases divided by total duration of observation on all patients in each two month section.

|   | BRONCHOSCOPY  |               |               |               |               |               |  |
|---|---------------|---------------|---------------|---------------|---------------|---------------|--|
|   | 6-4<br>months | 4-2<br>months | 2-0<br>months | 0-2<br>months | 2-4<br>months | 4-6<br>months |  |
| Single bronchoscopies   |               |               |               |               |               |               |  |
| Total months observation on all patients per two month section.....     | 200.30        | 248.70        | 287.40        | 284.90        | 260.00        | 230.00        | Patients: 149<br><br>Bronchoscopies: 149 |
| Total two months observation on all patients per two month section..... | 100.15        | 124.35        | 143.70        | 142.45        | 130.00        | 115.00        |  |
| Total number increases per two month section.....                       | 19            | 27            | 34            | 28            | 19            | 9             |  |
| Incidence (increases per two months).....                               | .19           | .21           | .25           | .20           | .15           | .08           |  |
| Multiple bronchoscopies   |               |               |               |               |               |               |  |
| Total months observation on all patients per two month section.....     | 123.20        | 150.30        | 196.90        | 497.50        | 242.30        | 159.50        | Patients: 84<br><br>Bronchoscopies: 324  |
| Total two months observation on all patients per two month section..... | 61.60         | 75.15         | 98.45         | 248.75        | 121.15        | 79.75         |  |
| Total number increases per two month section.....                       | 11            | 15            | 19            | 48            | 13            | 9             |  |
| Incidence (increases per two months).....                               | .18           | .20           | .19           | .19           | .11           | .11           |  |
| Whole group   |               |               |               |               |               |               |  |
| Total months observation on all patients per two month section.....     | 323.50        | 399.00        | 484.30        | 782.40        | 502.30        | 389.50        | Patients: 233<br><br>Bronchoscopies: 473 |
| Total two months observation on all patients per two month section..... | 161.75        | 199.50        | 242.15        | 391.20        | 251.15        | 194.75        |  |
| Total number increases per two month section.....                       | 30            | 42            | 53            | 76            | 32            | 18            |  |
| Incidence (increases per two months).....                               | .19           | .21           | .22           | .19           | .15           | .09           |  |

observation available on all patients (or patient-months) and the total number of increases can be obtained directly from the basic chart, as illustrated in figure 1. Figures for patient-months of observation are divided by two in each case, in

order to express the time in terms of two instead of one month intervals. Division of this figure into the total number of increases in the corresponding section then gives the *incidence* of increases for the two months in question. In sum, incidence may be said to represent the number of increases per two months' time which this group of patients showed in selected two month sections of their course.

By this method the incidence of increases in the two months immediately following bronchoscopy is compared to that in the other two month sections available for observation. As may be seen in table 1, the figures thus obtained show a uniform incidence of increases in the first four sections under observation. Thus it is apparent that no rise in incidence occurred in the two months immediately following the use of bronchoscopy.

The data were then considered from other points of view. First, the relationship of the type of lesion found at bronchoscopy to postbronchoscopic increases is shown in table 2. The 473 bronchoscopies were divided into two groups:

TABLE 2

*Relation of bronchoscopic findings to postbronchoscopic increase of disease*

| BRONCHOSCOPIC FINDINGS                 | GROUP A<br>73 BRONCHOSCOPIES<br>FOLLOWED WITHIN TWO<br>MONTHS BY ROENTGEN-<br>OGRAPHIC INCREASE OF<br>DISEASE |          | GROUP B<br>400 BRONCHOSCOPIES WITH<br>NO ROENTGENOGRAPHIC<br>INCREASE WITHIN TWO<br>MONTHS AFTER BRONCHOS-<br>COPY |          |
|--|---|----------|--|----------|
|  | Bronchoscopies  |          | Bronchoscopies   |          |
|  | Number  | Per cent | Number   | Per cent |
| Negative, or "healed disease".....     | 25  | 34.2     | 100  | 25.0     |
| "Bronchitis".....                      | 16  | 21.9     | 81   | 20.3     |
| Active endobronchial tuberculosis..... | 32  | 43.9     | 182  | 45.5     |
| Stenosis alone.....                    | 0   | 0.0      | 25   | 6.2      |
| Uncertain or no report.....            | 0   | 0.0      | 12   | 3.0      |
| Totals.....                            | 73  | 100.0    | 400  | 100.0    |

Group A comprises 73 bronchoscopies which were followed within two months by roentgenographic evidence of increase of disease; and Group B, the remaining 400 bronchoscopies following which no change for the worse took place. The pathological changes seen by the bronchoscopist were classified as follows: (1) *negative*, or "healed scars"; (2) "*bronchitis*", the term generally used by the bronchoscopist to describe nonspecific inflammation of the mucosa when etiology was in doubt; (3) *active endobronchial tuberculosis*, cases showing ulceration, granulation, or inflammation with edema interpreted as definitely tuberculous; (4) *stenosis alone*, those patients in whom a stricture was present without evidence of active tuberculosis; and (5) *uncertain*, a small group in which no reliable reports were available.

The proportion of these five types of bronchial findings was essentially the same in the two groups. Of particular interest is the fact that the group which developed increases within two months following bronchoscopy did not have a

higher incidence of active endobronchial disease than had the group which showed no progression of disease after bronchoscopy.

In table 3, the group of 59 patients who showed increases within two months after bronchoscopy is compared to the remaining 174 patients as regards extent of disease. The results revealed that the group with postbronchoscopic increases

TABLE 3

*Relation of extent of pulmonary tuberculosis to postbronchoscopic increase of disease*

| NATIONAL TUBERCULOSIS ASSOCIATION CLASSIFICATION<br>(AT TIME OF BRONCHOSCOPY) | GROUP A<br>59 PATIENTS HAVING ROENT-<br>GENOGRAPHIC INCREASE<br>WITHIN TWO MONTHS AFTER<br>BRONCHOSCOPY |          | GROUP B<br>174 PATIENTS WITH NO ROENT-<br>GENOGRAPHIC INCREASE<br>WITHIN TWO MONTHS AFTER<br>BRONCHOSCOPY |          |
|---|---|----------|---|----------|
|   | Bronchoscopies  |          | Bronchoscopies  |          |
|   | Number  | Per cent | Number  | Per cent |
| Minimal.....  | 4   | 6.8      | 16  | 9.2      |
| Moderately advanced.....  | 48  | 81.3     | 115   | 66.1     |
| Far advanced.....   | 7   | 11.9     | 43  | 24.7     |
| Totals.....   | 59  | 100.0    | 174   | 100.0    |

TABLE 4

*Incidence of roentgenographic increase of disease in two months following bronchoscopy in patients with and without prebronchoscopic increases*

|  | GROUP A<br>35 PATIENTS HAVING<br>ROENTGENOGRAPHIC IN-<br>CREASE WITHIN TWO<br>MONTHS BEFORE<br>BRONCHOSCOPY | GROUP B<br>114 PATIENTS WITH NO<br>ROENTGENOGRAPHIC IN-<br>CREASE WITHIN TWO<br>MONTHS BEFORE<br>BRONCHOSCOPY |
|--|---|---|
| Data on two months immediately following bron-<br>choscopy:                |   |   |
| Total months observation on all patients per two<br>month section.....     | 64.40   | 222.40  |
| Total two months observation on all patients per<br>two month section..... | 32.20   | 111.20  |
| Total number increases per two month section...                            | 6   | 22  |
| Incidence (increases per two months).....                                  | .19   | .18   |

Analysis of 149 patients bronchoscoped only once.

Incidence of increase of disease equals total number of increases divided by total duration of observation on all patients, in two month section.

(Group A) had less far advanced disease (11.9 per cent) than had the group with no increases after bronchoscopy (24.7 per cent of far advanced disease in Group B).

The incidence of increases in the two months preceding bronchoscopy was considered of interest in an effort to determine to what extent this influenced increase of disease after bronchoscopy. The group for study of this problem was limited

to 149 patients bronchoscoped only once (table 4), as inclusion of those having multiple bronchoscopies would have introduced difficult problems in regard to time intervals. Division again was made into two groups: Group A, comprising 35 patients all of whom had roentgenographic evidence of extension of the disease within two months preceding bronchoscopy; and Group B, 114 patients who showed no progression during this period. The incidence of increases in the two month period following bronchoscopy was computed for each of these groups in the manner described above. It was found to be essentially the same for both groups.

#### COMMENT

The evaluation of factors affecting the natural evolution of a chronic relapsing disease has always been difficult. As this is particularly true of pulmonary tuberculosis, a statistical plan of approach was adopted for this study in the belief that most informative results could be obtained in this way. Regarding the results, chief emphasis should be laid on the fact that bronchoscopy did not appear to affect over-all incidence of increases in this group of patients. The incidence was the same in the two months immediately following bronchoscopy as in similar periods of time preceding the procedure. As will be noted, there is a lowered incidence of increases in the last two sections under observation. This may have resulted, in part at least, from the frequent initiation of collapse therapy following bronchoscopy and from the fact that many patients were discharged as improved during or shortly after the observation period.

In regard to the extent of the disease as related to postbronchoscopic increases, it is of interest that the data obtained from this series revealed no tendency for postbronchoscopic increases to occur more readily in advanced cases; nor did progression of the disease shortly before bronchoscopy lead to a higher incidence of increases in the two months following the procedure.

A few additional points should be mentioned. The first of these is a consideration of the skill of the operator. This factor is undoubtedly an important one in the evaluation of any group of postbronchoscopic reactions. In the present series, a consistent high standard of ability was maintained, as all of the bronchoscopies were performed by one or the other of three well qualified men<sup>4</sup>.

The development of atelectasis has been reported as an occasional complication of bronchoscopy. In the present series this occurred, roentgenographically, in only one of the 73 cases of postbronchoscopic increase. Similarly, bronchoscopic dilatation of a stricture was performed only once in these 73 cases, although it was done on numerous occasions in the remainder without apparent ill effect. Other observers (12, 13) have described repeated bronchoscopic treatment of tuberculous stenotic bronchi without apparent harm to the patient.

As to the question of bronchoscopy as a cause of extension of pulmonary disease, no thoughtful student of tuberculosis will deny that reactivations, which on clinical grounds must be attributed to the procedure, can and do occur. The

<sup>4</sup>Dr. Edward S. Welles, Dr. Warriner Woodruff, Saranac Lake, New York; Dr. Winfield O. Kelley, Norwich, Connecticut.

literature contains no reliable data on the frequency with which this accident may happen. A statistical method has seemed necessary to investigate the problem, and the results should afford at least an approximation to the true picture.

#### SUMMARY

1. The literature on bronchoscopy in pulmonary tuberculosis contains little information on the frequency of progression of the pulmonary disease following instrumental examination of the bronchial tree.

2. In a series of 473 bronchoscopies in 233 patients at Trudeau Sanatorium, the incidence of roentgenographic increase of disease in the two months immediately following bronchoscopy was no greater than that in other two month periods before bronchoscopy.

3. Bronchoscopic findings in 73 bronchoscopies followed within two months by roentgenographic increase, as compared to those in 400 cases not showing such a postbronchoscopic increase, revealed essentially the same percentage of active endobronchial tuberculosis in the two groups.

4. In a group of 59 patients who had roentgenographic evidence of increase of disease within two months after bronchoscopy, the percentage of cases with far advanced disease was no greater than in the remaining 174 patients who showed no such postbronchoscopic increases.

5. The effect of progression of the disease before bronchoscopy on the course immediately after bronchoscopy was investigated in the group of 149 patients bronchoscoped only once. Thirty-five of these patients showed roentgenographic evidence of progression within two months preceding bronchoscopy, 114 did not. In these two groups the incidence of roentgenographic increases in the two months following bronchoscopy was essentially the same.

#### SUMARIO

##### *La Broncoscopia en la Tuberculosis Pulmonar*

1. La literatura relativa a la broncoscopia en la tuberculosis pulmonar contiene poca información acerca de la frecuencia de la agravación de la afección pulmonar después del examen instrumental del árbol bronquial.

2. En una serie de 473 broncoscopias realizadas en 233 enfermos del Sanatorio Trudeau, el aumento radiográfico de la enfermedad en el bimestre inmediatamente consecutivo a la broncoscopia no fué mayor que en otros bimestres anteriores a la broncoscopia.

3. Los hallazgos broncoscópicos en 73 broncoscopias seguidas en término de dos meses de agravación radiográfica, comparados con los de 400 casos que no mostraron tal agravación postbroncoscópica, revelaron toscamente el mismo por ciento de tuberculosis endobronquial activa en los dos grupos.

4. En un grupo de 59 enfermos que mostraron signos radiográficos de aumento de la enfermedad en término de dos meses de la broncoscopia, el porcentaje de casos con enfermedad muy avanzada no fué mayor que en los restantes 174 enfermos que no mostraron tales aumentos radiográficos.



5. En el grupo de 149 enfermos broncoscopiados una sola vez, se investigó el efecto de la agravación prebronconeoscópica de la enfermedad sobre la evolución inmediatamente después de la broncoscopia. Treinta y cinco revelaron signos radiográficos de agravación en término de dos meses antes de la broncoscopia, y 114 no los revelaron. En esos dos grupos la incidencia de agravación radiográfica en los dos meses subsiguientes a la broncoscopia fué en el fondo inéntica.

#### *Acknowledgment*

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# MODIFICATIONS OF TUBERCULOUS LESIONS IN PATIENTS TREATED WITH STREPTOMYCIN<sup>1,2,3,4</sup>

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## INTRODUCTION

This report describes the modifications of tuberculous lesions seen at autopsy in seven patients who had been treated with streptomycin. Each of these had generalized miliary tuberculosis as a complication of some visceral form of the disease. During their treatment with streptomycin each responded for a period of time which varied from about three weeks to many months. In five patients death was caused by an exacerbation of the visceral disease, and in two by chronic tuberculous meningitis. In each instance evidence of healing was seen in the miliary tubercles in the lungs and liver, and often in other viscera as well.

A previous report by Baggenstoss, Feldman, and Hinshaw (1) on the effect of streptomycin on the lesions of generalized miliary tuberculosis has been published, and the findings are in general accord with ours. The differences consist in the degree of healing observed and in certain modifications of the tuberculous lesions hitherto not described.

## MATERIAL AND METHODS

The clinical history of each case, the effects of the streptomycin therapy, and the principal gross and microscopic findings of the autopsy have been summarized.

In previous communications (2, 3) the clinical, bacteriologic, and roentgenologic aspects of these infections were presented in detail. As the same code names have been used, an exact correlation can be made between the previous and the present reports.

In each autopsy blocks were taken of at least four of the five lobes of the lungs and of the other viscera. Sections were stained as routine with hematoxylin-eosin, and frequently for connective tissue by the Masson-Goldner method as modified by Foot (4). Whenever the text describes "acid-fast bacilli" or "tubercle bacilli", the sections also were stained by the Ziehl-Neelsen method.

Criteria of activity of the tuberculous process were difficult to establish with certainty. In general, the presence of tubercle bacilli, recent areas of necrosis, tubercles composed of epithelioid cells or giant cells, was considered as indicating activity; the presence of abundant fibrosis and absence of cellular reaction were taken as indications of healing.

<sup>1</sup> From the Departments of Pathology and Medicine of Cornell University Medical College and the New York Hospital.

<sup>2</sup> Presented in part at the forty-fourth annual meeting of the American Association of Pathologists and Bacteriologists, Chicago, May 16, 1947 (*Amer. J. Path.*, 1947, 23, 874), and also at the inaugural session, Section on Microbiology, New York Academy of Medicine, November 25, 1947 (*Bull. New York Acad. Med.*, 1948, 24, 132).

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<sup>4</sup> This study was also aided by grants from Charles Pfizer and Co., Brooklyn, New York, and the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

## REPORT OF CASES

*Case 1 (P.Bu.) (Clinical summary:* The patient was an 18-month-old infant with an illness characterized by enlargement of cervical and mediastinal lymph nodes, roentgenologically demonstrable miliary densities in the lung, and the presence of acid-fast bacilli on direct examination of the gastric washings.

Streptomycin therapy was started on January 4, 1946, and consisted of 0.65 gm. daily, administered in divided doses, for a total period of five weeks.

Within ten days of the start of therapy, the circumference of the neck had receded from 28.5 to 20 cm. At the completion of the five weeks' course of treatment, roentgenologic examination revealed a conspicuous clearing of the miliary densities. After a twelve day interval, during which the patient became progressively more febrile, the same regimen of streptomycin therapy was again started. On February 28, fifty-four days after institution of the first course of streptomycin, the presence of tuberculous meningitis was established by characteristic spinal fluid changes, including a positive culture, despite the absence of clinical signs of meningeal irritation. Accordingly, the patient also received 51 intrathecal injections of 0.05 or 0.1 gm. of the drug during an eight week period which ended on May 12 (nine days after the last isolation of tubercle bacilli from the cerebrospinal fluid). Intramuscular streptomycin was discontinued on May 31, and the patient was discharged on June 23.

During the seven weeks after the cessation of therapy there were no evidences of either meningeal or miliary tuberculosis on clinical, roentgenological, and bacteriological examination, although the cerebrospinal fluid sugar was 34 mg. per cent at discharge. A marked impairment of hearing was present and there was definite ataxia.

Eight weeks after the completion of the antimicrobial therapy the patient was readmitted in coma and presented clinical and bacteriologic findings of tuberculous meningitis. Streptomycin therapy was reinstituted by both the intramuscular and the intrathecal routes. The patient never regained consciousness, internal hydrocephalus became evident, and she died thirteen weeks later on November 4, 1946, ten months after the original institution of streptomycin treatment. *There was no evidence of relapse of the miliary tuberculosis.*

Tubercle bacilli could be isolated intermittently from the cerebrospinal fluid throughout the greater part of the episode of asymptomatic meningitis and during the first two weeks of the subsequent clinically evident meningeal infection. Subsequent cultures were sterile. Repeated cultures and direct examinations of the gastric washings during the last eight months of life failed to reveal the presence of tubercle bacilli. All of the cultures isolated from the cerebrospinal fluid were inhibited *in vitro* by streptomycin concentrations of 5.0 micrograms per cc. of medium.

*Gross pathological findings (Autopsy No. 12164):* In the right lower lobe was a depressed area overlying a  $1 \times 1.5$  cm. very firm nodule. At the right hilum were five grey-yellow, firm lymph nodes, each measuring 1.0 cm. in diameter. On section, all of these nodules

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FIG. 1. Case 1. Healed miliary tubercles in lung. Each small scar is a healed tubercle. Their distribution in the lung tissue is quite uniform and similar areas are seen in all lobes of the lungs. No active tubercles are found.  $\times 25$ .

FIG. 2. Case 1. Healed miliary tubercle in lung. The lesion is composed of a loose network of collagen and reticulum fibers in which are scattered macrophages, lymphocytes, and often several capillaries. No giant cells, areas of caseation, or acid-fast bacilli are found in these lesions.  $\times 180$ .

FIG. 3. Case 1. Healed miliary tubercles in lung. Reticulum stain.  $\times 50$ .

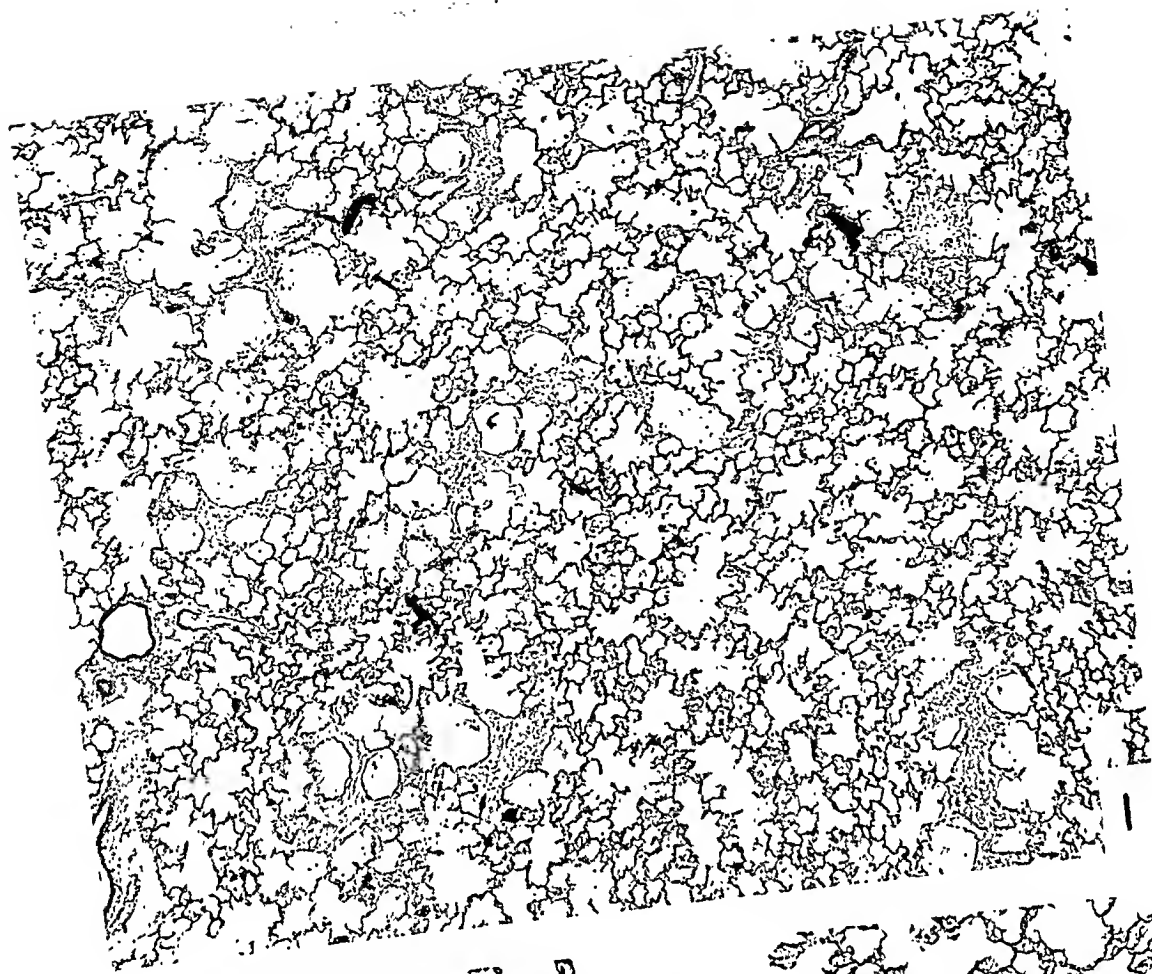


FIG. 2.

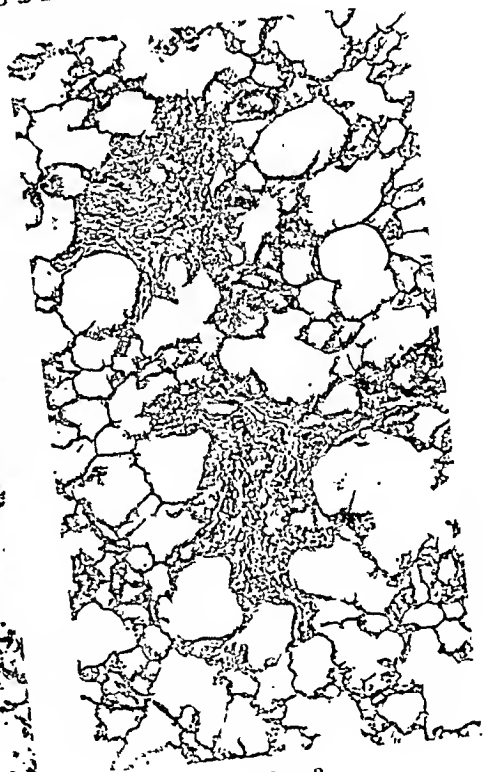
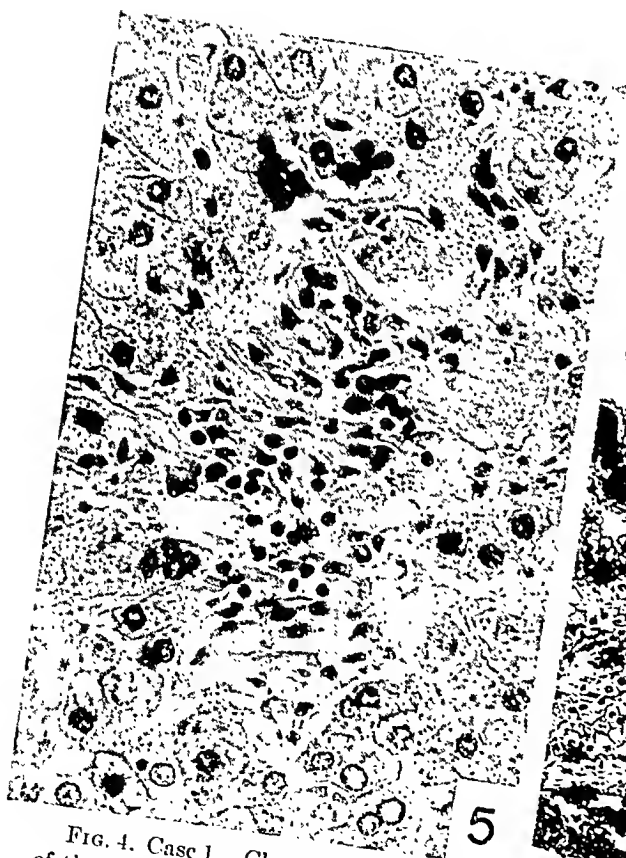


FIG. 3.



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FIG. 4. Case 1. Chronic tuberculous meningitis. The section is taken through the level of the pons and includes the basilar artery. The pia-arachnoid is replaced by a mass of loose collagen in which are many macrophages, monocytes, and some lymphocytes. No areas of caseation, giant cells, or acid-fast bacilli are seen, and no organisms were recovered by cultural methods.  $\times 35$ .

FIG. 5. Case 1. Healed miliary tubercle in liver. The lesion is composed of dense collagen in which are some macrophages and lymphocytes. These lesions are less numerous than those in the lungs.  $\times 450$ .

FIG. 6. Case 1. Tubercle in the choroid plexus. Many similar tubercles are found in this structure. All have a small central area of caseation surrounded by a dense fibrous capsule. No acid-fast bacilli or giant cells are seen.  $\times 140$ .

contained yellow-white, firm, caseous material in which was some calcification. About each nodule was a thick fibrous capsule. No other nodules or scars could be seen in the lungs. The liver, spleen, kidneys, and adrenals contained no visible tubercles.

The convolutions of the hemispheres of the brain were flattened, and there was slight thickening of the arachnoid over the cortex and marked thickening over the interpeduncular space and over the pons and medulla. Internal hydrocephalus was marked. On section, no tubercles were seen in the brain.

*Postmortem bacteriologic examination:* Cultures of the lung tissue, made at a distance from the calcified tubercle, and of the brain and ventricular fluid were sterile.

*Microscopic observations:* The peripheral portion of the primary complex in the lung was a partly calcified caseous mass surrounded by a dense fibrous capsule. The hilar lymph nodes were similar. There was no evidence of activity in these lesions.

Many focal scars, presumably healed miliary tubercles, were seen in the lungs (figures 1, 2, and 3), and some in the liver (figure 5). Acid-fast stains failed to reveal bacilli in these scars. No scars were identified in the spleen. No miliary tubercles containing areas of caseation or giant cells were seen in the lungs, liver, or spleen.

There was a marked chronic healing tuberculous meningitis (figure 4) with extensive fibrosis and many macrophages and lymphocytes but no areas of necrosis. Some fibrous proliferation of the intima of the vessels was noted. Small tubercles with caseous centers were found in the choroid plexus (figure 6). No acid-fast bacilli were seen in these lesions.

#### *Anatomical diagnoses:*

Healed primary tuberculous complex with encapsulated calcified areas in the lung and lymph node.

Healed mediastinal lymph node tuberculosis with encapsulation and calcification.

Healed generalized miliary tuberculosis with focal scars in the lungs and liver.

Chronic tuberculous meningitis with marked internal hydrocephalus, marked fibrosis of the meninges, and arteritis.

### Summary and Comment

This 18-month-old infant had had advanced tuberculosis of lymph nodes, miliary tuberculosis, and tuberculous meningitis. All clinical evidence of active disease disappeared under streptomycin therapy, but a marked chronic fibrous meningitis persisted, resulting in hydrocephalus and death eight months after its onset. At autopsy all lesions showed marked healing. The lungs and liver contained healed miliary tubercles. No tubercle bacilli were cultured from the lungs and brain, and none were seen on acid-fast stains of these organs.

*Case 2 (R.He.) Clinical summary:* The patient was a 17-month-old infant who had received twenty-three days of streptomycin therapy two months previously because of the presence of miliary tuberculosis. On admission to the hospital (February 20, 1947), he presented the characteristic clinical and roentgenologic picture of miliary tuberculosis with enlarged mediastinal nodes. Clinical signs of meningitis were also present and tubercle bacilli were cultured from the cerebrospinal fluid.

Streptomycin was administered for 124 days on a regimen of 0.6 gm. daily by the intramuscular route supplemented by 49 intrathecal injections of 0.05 or 0.1 gm.

After the institution of therapy, the cerebrospinal fluid cultures were sterile and there was clinical improvement accompanied by a complete clearing of the densities previously visible on the roentgenogram. Nevertheless, the cerebrospinal fluid sugar remained con-

sistently below 40 mg. per cent even at the time of discharge on August 6, 1947. One month later, tubercle bacilli were cultured from the fluid of a follow-up lumbar puncture and the patient was readmitted for further streptomycin therapy. His condition deteriorated rapidly, subarachnoid block developed, and he died on October 1, 1947, approximately nine months after the first streptomycin therapy. Roentgenologic examination of the chest one week before death revealed no evidence of a return of the miliary type densities. The cultures of tubercle bacilli obtained from the cerebrospinal fluid, both before intrathecal treatment and during the relapse, were inhibited *in vitro* by streptomycin concentrations of 2.0 micrograms per cc. of medium.

*Gross pathological findings* (Autopsy No. 12559): In the lower lobe of the right lung was a nodule, measuring 7.5 mm. in diameter, composed of partly calcified caseous material and surrounded by a thin fibrous capsule. In a hilar lymph node was a similar partly calcified mass measuring 2 cm. in diameter. The lungs, liver, spleen, adrenals, kidneys, and other lymph nodes contained no grossly visible tubercles or scars.

Over the base of the brain the leptomeninges were fibrous and thickened, obscuring the normal structures, and contained numerous miliary tubercles. There was marked enlargement of the lateral ventricles.

*Postmortem bacteriologic examination*: Cultures of the lung, liver, spleen, kidney, and mesenteric and hilar lymph nodes grew no bacilli. From the cerebral cortex and basilar meninges, tubercle bacilli were recovered which were sensitive to less than 1.0 microgram of streptomycin per cc. of culture medium.

*Microscopic observations*: The primary peripheral tubercle in the lung and the involved hilar lymph nodes consisted of partially calcified areas of caseous necrosis surrounded by a thin fibrous capsule. In some areas, however, there was recent caseation containing nuclear debris and surrounded by some epithelioid and giant cells. Although no acid-fast bacilli could be identified, the histological appearance of the lesion suggested activity of the tuberculous process.

In each of the lobes of the lungs and in the liver were many scattered focal scars of healed miliary tubercles similar to those seen in Case 1, and, in addition, a few miliary tubercles with caseous centers surrounded by epithelioid cells and a fibrous capsule. In the spleen were some poorly demarcated focal scars (figure 9) and a few active miliary tubercles. No acid-fast bacilli were seen in the scars or active lesions in these organs.

The chronic meningitis with many areas of activity is shown in figure 7. This consisted of masses of fibrous tissue containing focal areas of caseation, epithelioid cells, and many unusually large giant cells. A few larger encapsulated tubercles were also seen. A few acid-fast bacilli were found in the small tubercles. Several large meningeal arteries showed marked fibrous intimal thickening (figure 8).

#### *Anatomical diagnoses:*

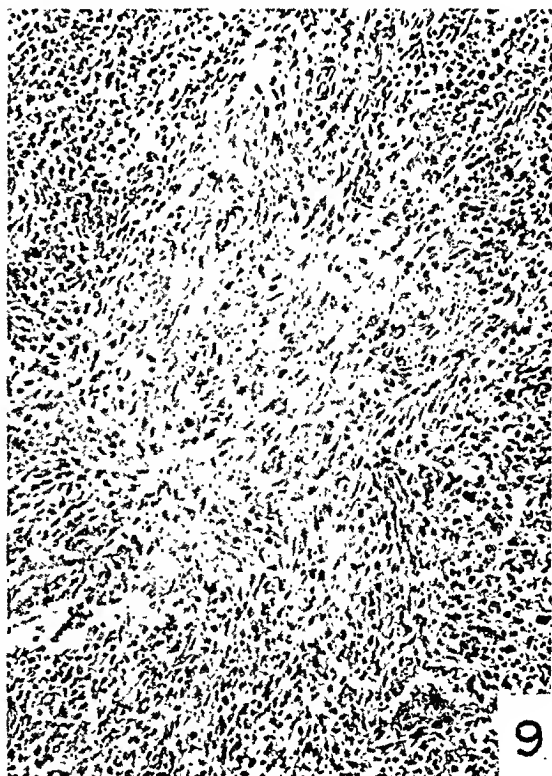
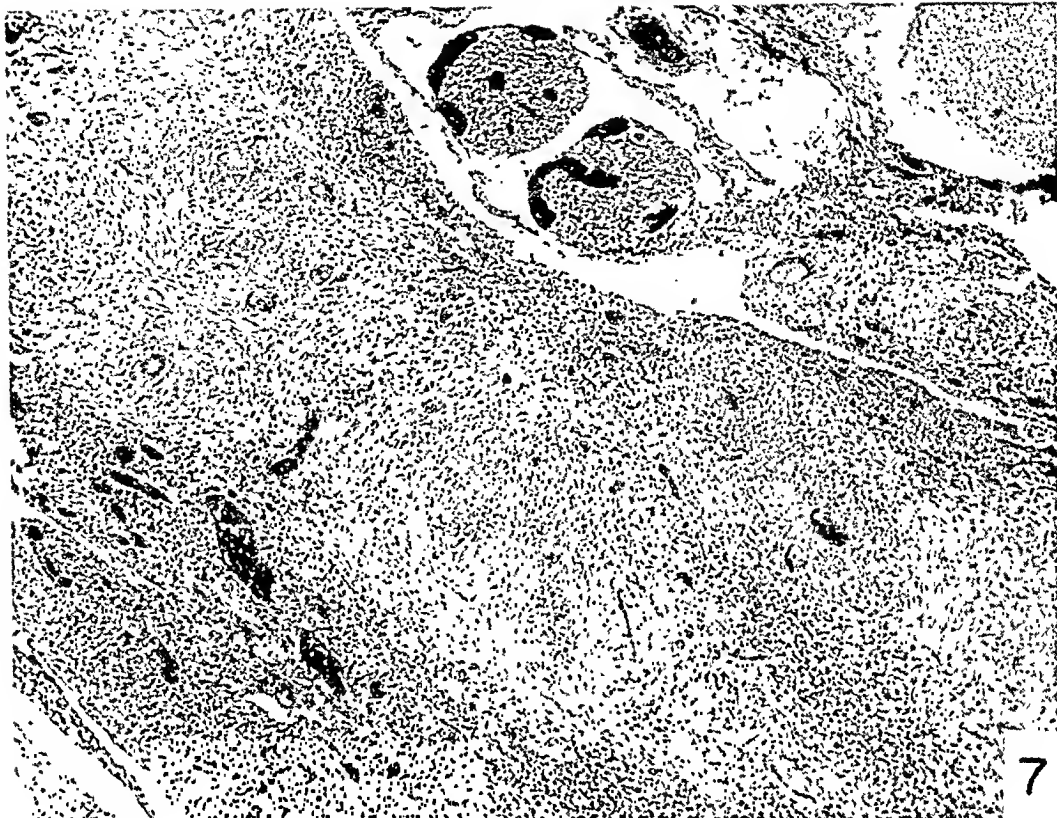
Partially healed primary tuberculous complex with calcified encapsulated but probably active tuberculous areas in the lung and lymph node.

FIG. 7. Case 2. Active chronic tuberculous meningitis. The section is through the meninges and nerve roots about the cervical cord. Many caseous areas are seen surrounded by giant cells and much dense fibrous tissue. A few acid-fast bacilli are identified in this tissue. Similar lesions are found in the meninges of the brain. In the meninges about the base of the brain are some large caseous tubercles surrounded by thick fibrous capsules.  $\times 50$ .

FIG. 8. Case 2. Arteritis in meninges of brain. The proliferative arteritis is marked in this case, with considerable reduction in the lumina of the vessels.  $\times 50$ .

FIG. 9. Case 2. Focal scar in spleen. Several of these are found, and they probably are healed miliary tubercles.  $\times 180$ .







Partially healed mediastinal lymph node tuberculosis.

Generalized miliary tuberculosis with many healed and a few probably active miliary tubercles in the lungs and liver and, to a lesser extent, in the spleen.

Active chronic tuberculous meningitis with marked internal hydrocephalus and marked fibrous endarteritis.

### Summary and Comment

This 17-month-old infant had mediastinal lymph node tuberculosis, generalized miliary tuberculosis, and tuberculous meningitis. With streptomycin therapy the miliary tuberculosis disappeared, as indicated by the roentgenograms of the chest; but the meningitis, though markedly improved, persisted, eventually causing death seven and a half months after its onset.

At autopsy the chronic meningitis showed evidence of extensive activity although the tubercle bacilli cultured from the meninges were still quite sensitive to streptomycin. A marked fibrous endarteritis was present in several large meningeal vessels. There were healed miliary tubercles in the lungs, liver, and spleen, but other tubercles seen in these organs appeared active despite the fact that no tubercle bacilli could be seen microscopically, and cultures were sterile.

*Case 3 (S.Le.) Clinical summary:* The patient was an 11-year-old Chinese female who was admitted to the hospital on November 23, 1946, with the characteristic clinical, roentgenologic, and bacteriologic manifestations of acute miliary tuberculosis accompanied by involvement of lymph nodes. Meningeal involvement was demonstrated by characteristic changes, including positive culture, in the cerebrospinal fluid, although clinical evidences of meningitis were absent.

Streptomycin was administered intramuscularly on a regimen of 1.8 gm. daily for sixty-eight days supplemented by 27 intrathecal injections of 0.1 gm.

During the first three weeks of antimicrobial therapy there was a marked clinical and roentgenologic improvement with virtually complete clearing of the miliary densities in the lungs. Despite the continuation of streptomycin, all of the clinical and roentgenologic manifestations of the disease returned during the second month of treatment. The infection steadily progressed, and the patient died on the sixty-eighth day of therapy. Deafness became evident before death.

The pretreatment cultures of tubercle bacilli from the cervical nodes were inhibited *in vitro* by 2.0 micrograms of streptomycin per cc. of medium. The first positive cultures after the start of treatment were obtained on the forty-second day and were not inhibited by 500 micrograms per cc. of medium. All subsequent cultures were also resistant.

*Gross pathological findings (Autopsy No. 12289):* In the upper lobe of the right lung was a large cavity surrounding which was a zone of tuberculous pneumonia. Scattered throughout the lungs were great numbers of tubercles measuring 3 mm. across; in many places these were conglomerate.

The cervical, mediastinal, abdominal, and some other lymph nodes were enlarged and filled either with caseous material or, in some instances, with liquid exudate. There were multiple tuberculous abscesses in the cervical, retroperitoneal, and pelvic tissues.

Great numbers of miliary tubercles were seen in the liver and spleen, and to a lesser extent in the kidneys and adrenal glands, and on the pericardial and peritoneal surfaces. In the lower intestines were many small ulcers. The arachnoid over the brain and cord was slightly thickened.

*Postmortem bacteriologic examination:* Cultures of the cervical abscess grew tubercle bacilli which were resistant to more than 500 micrograms of streptomycin per cc. of medium.

*Microscopic observations:* The large cavity in the right upper lobe was thin-walled and lined with caseous material. In the lung tissue elsewhere were the scars of healed miliary and larger tubercles (figures 10 and 11), cellular "soft" tubercles, and partially healed tubercles with fresh caseous areas in their substance or at one edge of the scar (figure 10).

In the lymph nodes were much recent caseous necrosis and early abscess formation. In the liver were scars of healed miliary tubercles and many soft caseous lesions. The spleen and kidney contained caseous tubercles. No tubercle bacilli could be identified in the scars in the lungs and liver, but in all caseous "soft" tubercles were large numbers of acid-fast bacilli.

There was a slight fibrous thickening (figure 12) of the pia-arachnoid containing lymphocytes and macrophages, and a few, small, poorly formed tubercles containing epithelioid cells and lymphocytes. There was a slight chronic ependymitis containing an occasional giant cell and a thickening of a few of the arterioles of the pia-arachnoid. No areas of caseation or arteritis were seen.

*Anatomical diagnoses:*

Primary pulmonary tuberculosis with cavity formation, tuberculous bronchitis, and tracheitis.

Generalized tuberculosis of lymph nodes with multiple tuberculous abscesses.

Tuberculous pericarditis, peritonitis, and enteritis.

Generalized miliary tuberculosis with caseous tubercles in the lungs, liver, spleen, and bone marrow, and the scars of healed tubercles in the lungs and liver.

Slight chronic tuberculous meningitis.

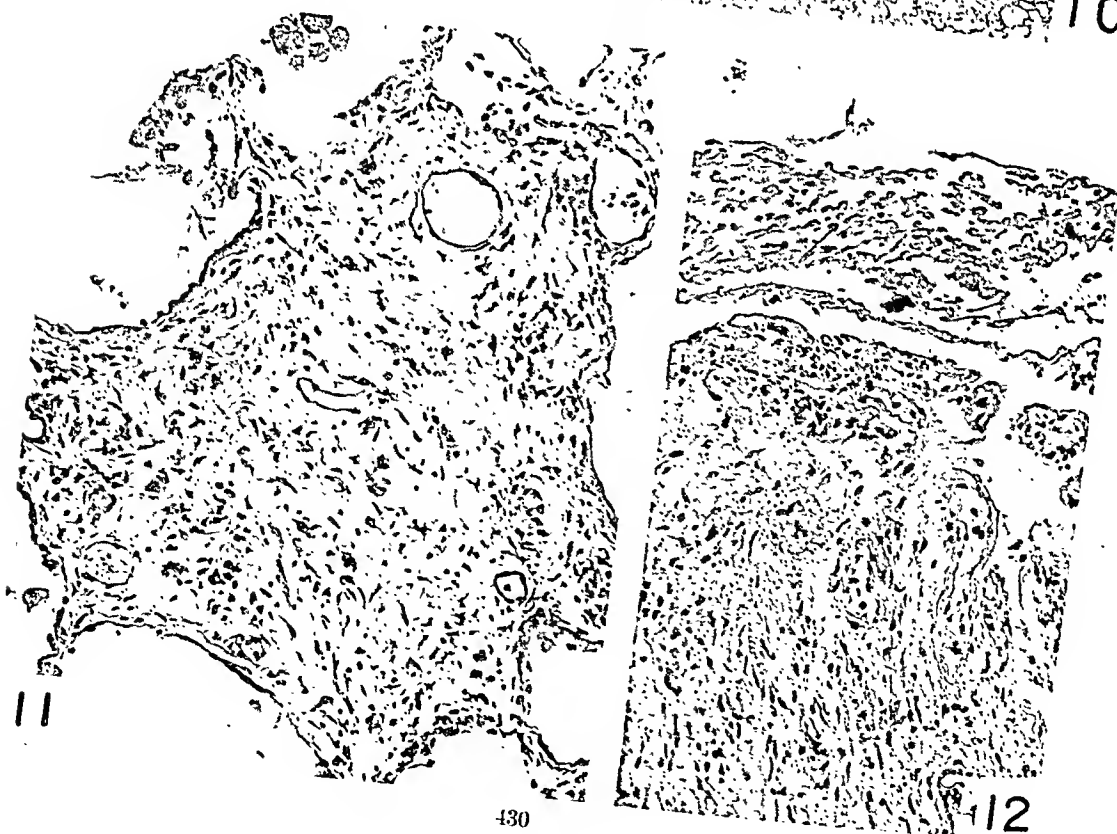
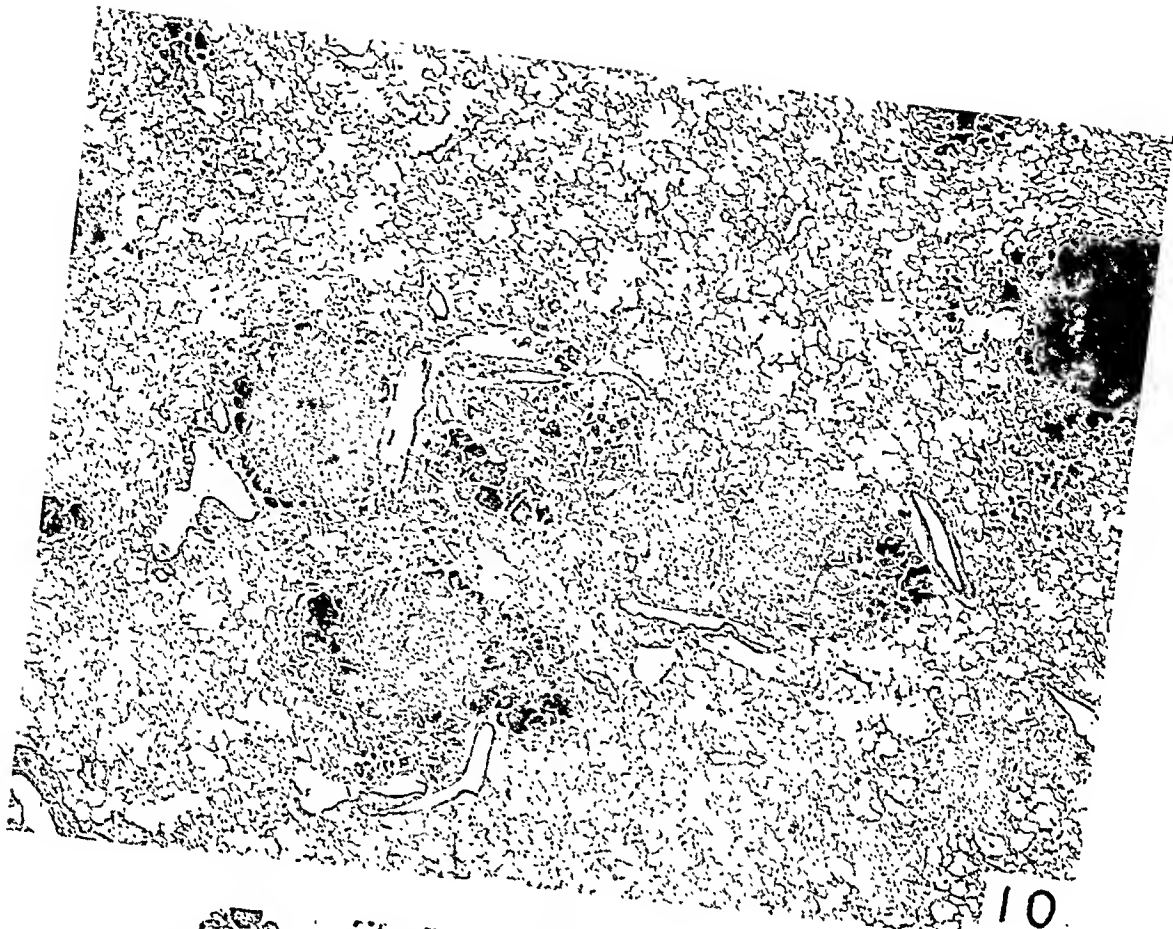
### Summary and Comment

An 11-year-old Chinese female developed massive lymph node tuberculosis with draining sinuses, generalized miliary tuberculosis, and tuberculous meningitis. She was treated with streptomycin with marked clinical improvement, but with subsequent rapid return of all processes except the meningitis, which did not recur clinically. During the therapy the sensitivity of the bacilli to streptomycin decreased markedly.

At autopsy there was far advanced tuberculosis with many bacilli in the caseous lesions. The evidence of healing consisted of scars in the lungs and liver and slight fibrous thickening of the leptomeninges. Some miliary tubercles in the lungs seemed to recur in partially healed scars.

*Case 4 (C.Co.) Clinical summary:* The patient was a 21-year-old white male who was admitted to the hospital on March 25, 1946, with lymph node tuberculosis and clinical roentgenologic and bacteriologic manifestations of acute miliary tuberculosis.

Streptomycin therapy was started immediately and consisted of the intramuscular administration of 3.0 gm. daily for a total period of five months. A dramatic clinical improvement followed the start of therapy. Minimal evidences of meningitis, without positive culture, which appeared on the thirty-fifth day, promptly subsided following the intrathecal administration of the drug, 0.1 gm. daily for the following month. During the third month of antimicrobial therapy, the patient presented no clinical, roentgeno-



logic, or bacteriologic evidences of his infection. Relapse first appeared at the beginning of the fourth month, and soon there was a return of the original manifestations of the disease. Despite the continuation of intramuscular streptomycin therapy, the infection continued to progress and terminated fatally on September 3, 1946, five months after the original institution of treatment. Impairment of hearing appeared during treatment.

Cultures of tubercle bacilli obtained from lymph nodes and gastric washings before treatment were inhibited *in vitro* by streptomycin concentrations of 1.0 microgram per cc. of medium. During the period of the remission of the infection, no bacilli were obtainable by culture. Cultures of tubercle bacilli obtained from lymph node and gastric washings at the onset of relapse were not inhibited by streptomycin concentrations of 1,000 micrograms per cc. of medium. All cultures obtained subsequently were similarly resistant to the action of streptomycin *in vitro*.

*Gross pathological findings* (Autopsy No. 12092): There was great enlargement of the cervical, mediastinal, and abdominal lymph nodes. Some nodes contained green liquid material; others, firmer caseous material. Below the left mandible were three large multilocular tuberculous abscesses. There was also a large retropharyngeal abscess. There were tremendous numbers of large miliary tubercles (0.5 to 3 mm. in diameter) scattered diffusely through the lungs, and in the liver and spleen. In these organs, and in the kidneys, adrenals, and thyroid were also tubercles of a larger size, reaching 4 mm. in diameter. There were small tubercles in the mucosa of the ileum and cecum with many areas of ulceration.

There were milkeness and some thickening of the arachnoid, most marked over the base of the brain. Several minute tubercles could be seen in the arachnoid. The lateral ventricles were slightly dilated. No tubercles were seen on thin sections of the brain.

*Postmortem bacteriologic examination*: Cultures of a cervical abscess and of the spinal fluid grew tubercle bacilli which were resistant to 1,000 micrograms of streptomycin per cc. of medium.

*Microscopic observations*: The lymph nodes were replaced by masses of necrotic debris surrounded by a thin wall of epithelioid cells and fibrous tissue. Acid-fast bacilli were abundant.

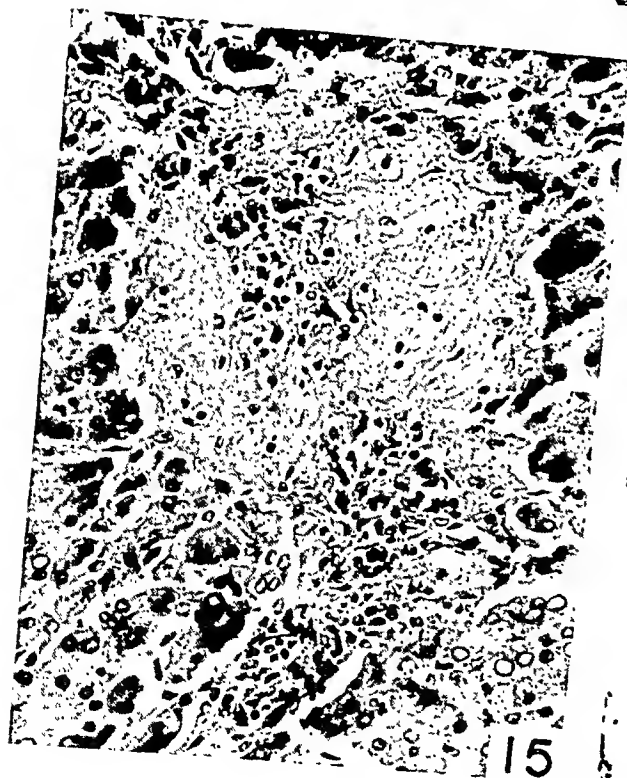
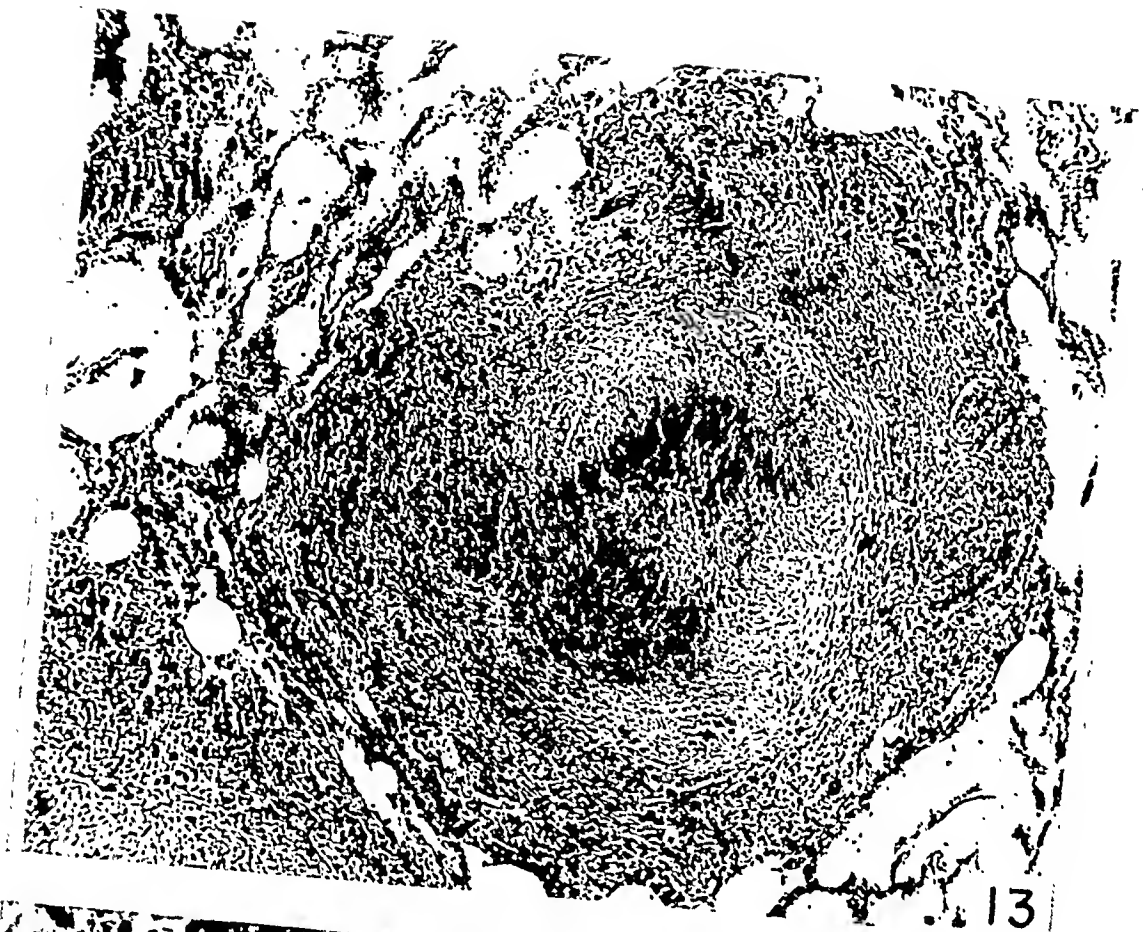
In all sections of the lung were very large miliary tubercles, most of which had a large center of recent caseous material surrounded by a thin ring of fibrous tissue (figure 13). Outside of this "ring" the tubercles varied: some were surrounded by many epithelioid cells, an occasional giant cell, and fibrous tissue, but around most was more necrosis and evidence of spread of the tuberculous process. All contained large numbers of acid-fast bacilli. In addition to these tubercles, there were some focal scars of healed miliary tubercles (figure 14).

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FIG. 10. Case 3. Active and healed miliary tubercles in lung. In this photomicrograph are several healed miliary tubercles and scattered large caseous miliary tubercles, one of which is adjacent to a large partially healed miliary tubercle. Many acid-fast bacilli are seen in the caseous material, but none in the focal scars.  $\times 25$ .

FIG. 11. Case 3. Healed miliary tubercle in lung. The lesion is composed of loosely arranged collagen, some macrophages, lymphocytes, and a few capillaries.  $\times 180$ .

FIG. 12. Case 3. Slight chronic tuberculous meningitis. The section is through the meninges at the base of the brain. The pia-arachnoid is slightly thickened and contains some macrophages and foci of lymphocytes. Elsewhere are a few poorly formed tubercles containing some epithelioid cells but no areas of caseation. The walls of some of the arterioles in the pia-arachnoid are thickened. There is also a slight chronic ependymitis containing an occasional giant cell.  $\times 180$ .



In the liver were active tubercles and some focal scars (figure 15). Active military tubercles were seen in the spleen and other organs. In the ileum were early tuberculous ulcers.

In the arachnoid over the cerebral cortex and pons was a slight exudate of polymorphonuclear leukocytes, macrophages, and lymphocytes, with early tubercle formation.

*Anatomical diagnoses:*

Massive caseating lymph node tuberculosis of the cervical, mediastinal, and abdominal lymph nodes; multiple tuberculous abscesses in the neck.

Generalized military tuberculosis, with extension of most tubercles, but with evidence of healing in the lungs and liver; tuberculous enteritis; and early tuberculous meningitis.

### Summary and Comment

A 21-year-old male developed rapidly progressive tuberculosis of lymph nodes and generalized military tuberculosis. Streptomycin therapy was accompanied by rapid clinical improvement. After one month, slight meningitis without positive spinal fluid culture developed and disappeared under treatment with intrathecal streptomycin. In the fourth month of therapy relapse began and was progressive. During the course of therapy the tubercle bacilli became very resistant to streptomycin.

At autopsy the only evidences of modification were seen in the rings of fibrous tissue in tubercles found in the lungs and in the scars of healed military tubercles seen in the lungs and liver. In the remainder of the lesions the disease was progressive.

*Case 5 (H.Cl.) Clinical summary:* The patient was a 44-year-old white male who was admitted to the hospital on December 30, 1945. Twenty months previously he had had a left nephrectomy for renal tuberculosis. The present illness was characterized by continued fever, splenomegaly, roentgenologically demonstrable military densities throughout both lungs, and choroidal tubercles.

It was never possible to culture tubercle bacilli from the various discharges of the patient examined during life.

Streptomycin therapy (3.0 gm. daily) was started on January 27, 1946, and was discontinued at the end of fifty-four days because of evidence of impaired renal function.

The patient became afebrile shortly after the start of antimicrobial therapy. During the period of drug treatment and the four months thereafter, he continued to improve and the military densities could no longer be visualized on the roentgenogram. An easy fatigability persisted and in August 1946, four months after the cessation of therapy, a relapse occurred, characterized by a return of fever and the military densities in the lungs demonstrable on the roentgenogram.

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FIG. 13. Case 4. Active military tubercle in lung. In the center of the lesion is a mass of caseous material partially surrounded by a ring of collagen which appears light-colored in the photomicrograph. Outside of this is another area of recent caseous necrosis. Acid-fast bacilli are abundant in the caseous material.  $\times 50$ .

FIG. 14. Case 4. Healed military tubercle in lung. Only a few of these scars are found in this case, though the clinical response to streptomycin was excellent.  $\times 140$ .

FIG. 15. Case 4. Healed military tubercle in liver. This is a dense scar containing a few macrophages and lymphocytes.  $\times 280$ .

Streptomycin (1.0 gm. daily) was reinstituted and continued for seventy days until November 15, 1946. At this time the patient appeared well and the milary densities had again disappeared. During this second course of streptomycin therapy, the patient became completely deaf and showed evidence of vestibular dysfunction. The impairment of renal function (urea clearance 13 per cent) did not obviously progress during this course of drug therapy and the blood urea nitrogen ranged between 30 and 40 mg. per cent.

Three weeks after completion of the streptomycin treatment, a second relapse of the infection occurred and drug therapy was reinstituted. His condition steadily grew worse, and the blood urea nitrogen rose to 105 mg. per cent. The patient died on December 12, 1946, apparently as a result of a combination of the infection and the renal insufficiency.

*Gross pathological findings* (Autopsy No. 12222): The left kidney was absent, but at its site was an encapsulated caseous and calcified mass measuring 2 by 2 by 4 cm. In the mesentery was a calcified lymph node. Scattered throughout all lobes of the lungs were many tiny nodules. Most of the lung tissue was slightly gray and firmer than normal. The hilar lymph nodes were uninvolved.

The spleen and the liver contained no visible tubercles. In the medullary portion of the right kidney were many round, pinhead sized nodules.

*Postmortem bacteriologic examination*: Cultures of the lung yielded a slowly growing strain of tubercle bacilli which grew so poorly on artificial media that satisfactory *in vitro* drug sensitivity studies could not be performed. At least some of the bacterial cells, however, were not inhibited by streptomycin concentrations of 10 micrograms per cc. of medium, but were inhibited by concentrations of 100 micrograms. Cultures of the kidney, spleen, left renal mass, ventricular fluid, and brain grew no tubercle bacilli.

*Microscopic observations*: The alteration of the parenchyma of the lungs is shown in figure 16. This was seen in all lobes and is best interpreted as an unusual type of chronic tuberculous pneumonia, characterized by the presence in the alveoli of fibrous tissue, macrophages, large giant cells (figure 17), and focal areas of caseation. The endo-angiitis (figures 16 and 18) was striking and involved many small vessels, some of which were thrombosed. Many focal scars of healed milary tubercles were also seen.

There were a large number of small scars in the liver (figure 21), a few scars in the spleen and in both the liver and spleen many small tubercles containing caseous areas and a few acid-fast bacilli.

In the kidney were many small rounded scars having the general shape of small healed tubercles and composed of fibrous tissue and lymphocytes, areas of more diffuse fibrosis containing giant cells, and a few active milary tubercles. There were also several larger encapsulated tubercles (figure 20). The renal tubules showed some degeneration.

In the pons were several healing tubercles (figure 19). There was no meningitis.

#### *Anatomical diagnoses:*

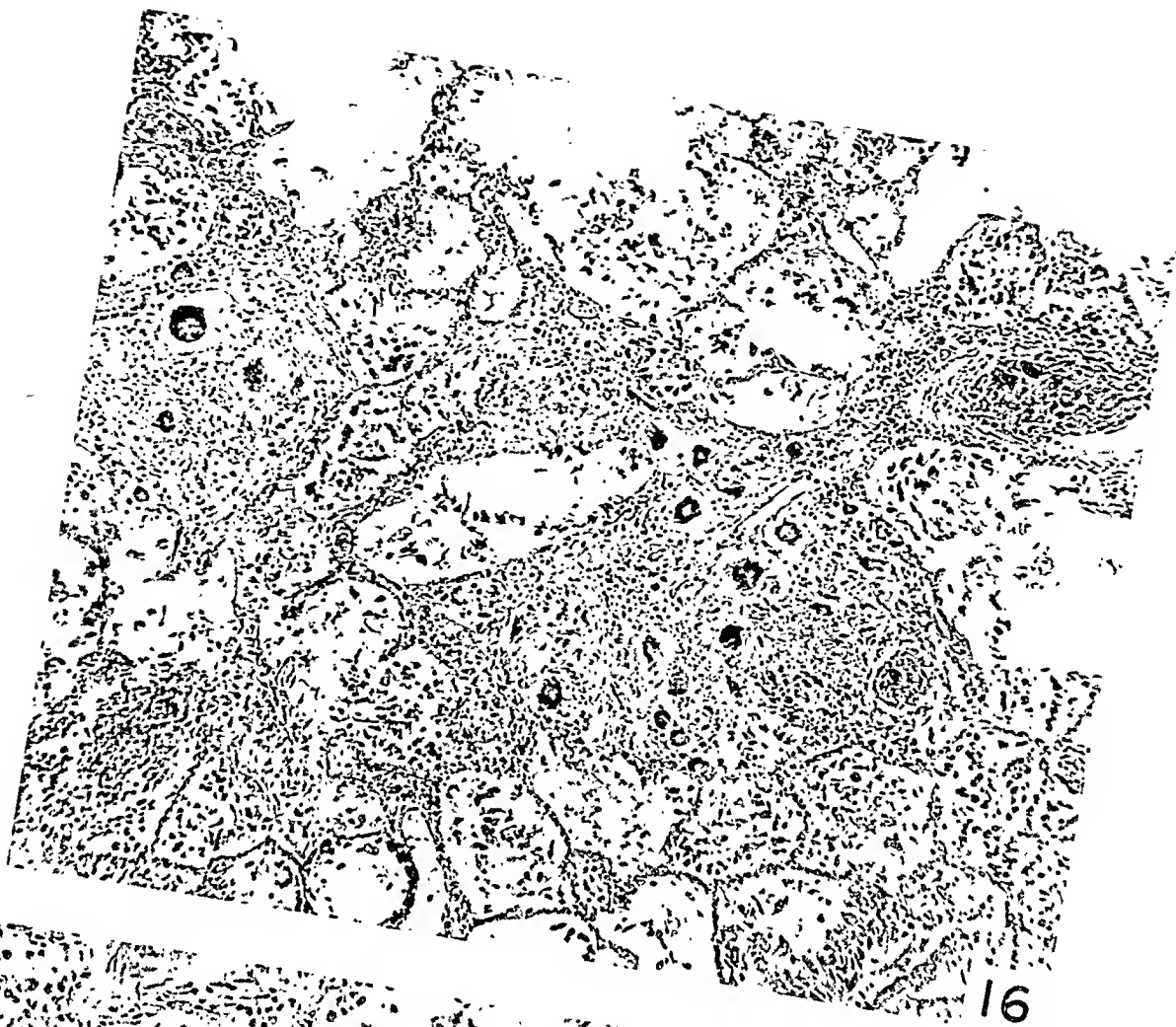
Renal tuberculosis, with surgical absence of the left kidney and healing caseonodular tubercles in the right kidney.

FIG. 16. Case 5. Chronic tuberculous pneumonia. The alveoli are filled with fibrous tissue, macrophages, and large giant cells. In some alveoli are focal areas of caseation in which a few acid-fast bacilli can be seen. In many of the small arteries and veins is a tuberculous endoangiitis, and two involved vessels can be seen in this photomicrograph.  $\times 50$ .

FIG. 17. Case 5. Giant cells in pneumonia. The tremendous giant cells and the infiltration of the alveoli are shown.  $\times 180$ .

FIG. 18. Case 5. Tuberculous endoangiitis. There is a mass of tuberculous inflammatory tissue projecting from the intima into the lumen of the vessel.  $\times 180$ .





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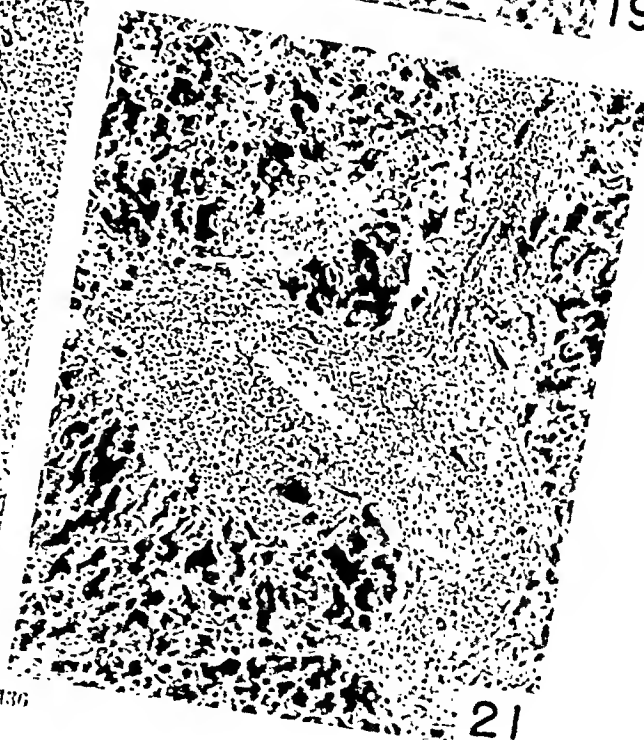
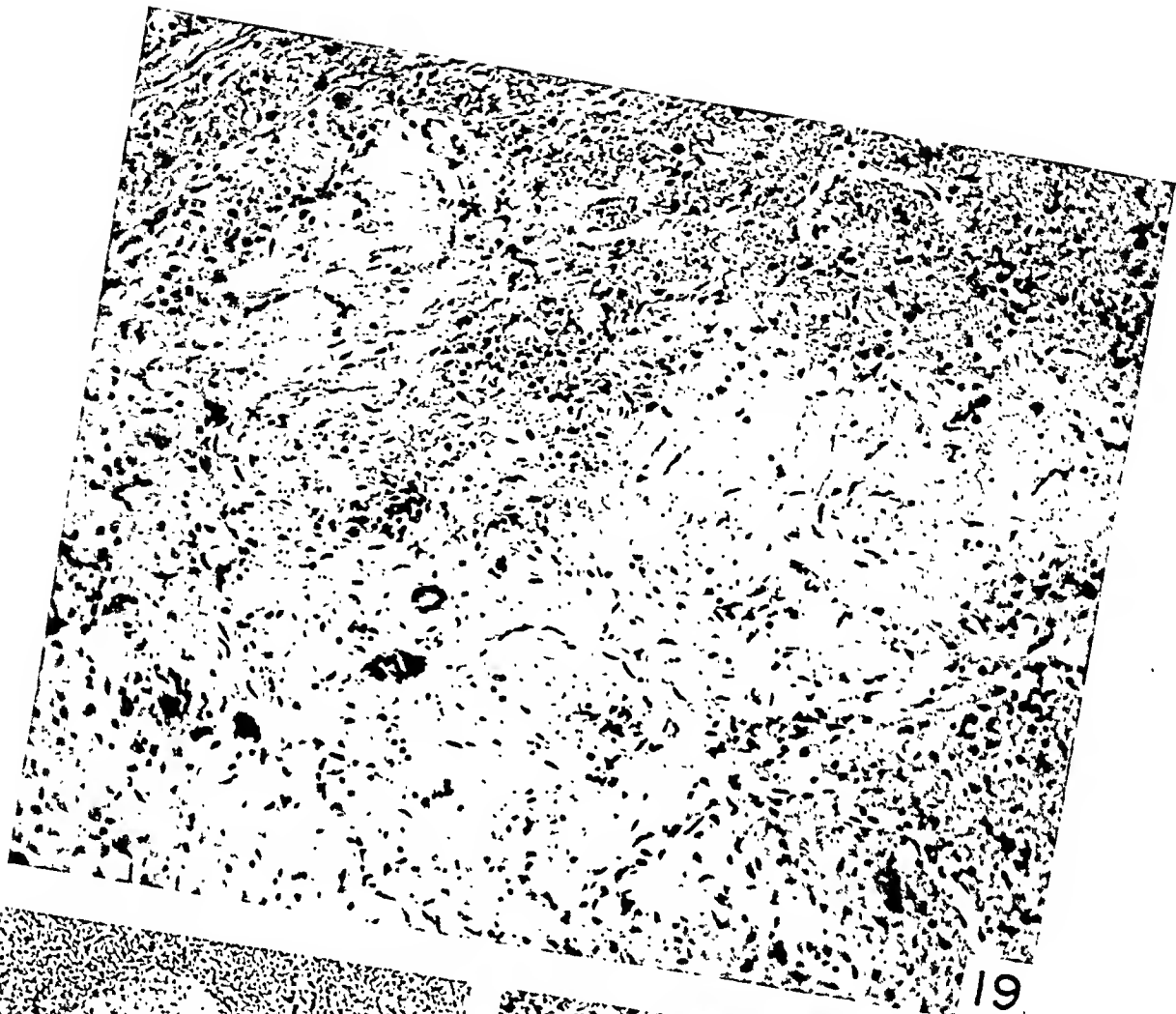


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Generalized miliary tuberculosis with active miliary tubercles in the lungs, liver, spleen, and kidney, healed miliary tubercles in the lungs, liver, and kidney, and healing small tubercles in the brain.

Diffuse chronic tuberculous pneumonia, with tuberculous endoangiitis.

### Summary and Comment

A 44-year-old man, who developed miliary tuberculosis following nephrectomy for renal tuberculosis, had an excellent response to streptomycin therapy on two occasions. Renal insufficiency was prominent during the clinical course.

At autopsy the scars of healed miliary tubercles were seen in the lungs, liver, spleen, and brain. The diffuse, chronic, pneumonia-like process in the lungs probably resulted from extension from the miliary tuberculosis. The frequency of the endoangiitis was unusual. It is of interest that the tubercle bacilli recovered from the lungs postmortem, the only bacilli ever cultured in this case, grew very poorly on artificial media.

In view of the extensive diffuse tuberculous involvement of the kidney, it is doubtful that streptomycin played a great role in the renal failure.

*Case 6 (E.De.) Clinical summary:* The patient was a 19-year-old white female who was admitted to the hospital on July 31, 1946, with actively progressing tuberculosis of lungs, cervical lymph nodes, epiglottis, and pharynx of four months' duration. The involvement of these structures was evident on admission, as well as the presence of disseminated miliary densities in the lungs on the roentgenogram, and choroidal tubercles.

During the first two months of streptomycin therapy (3 gm. daily in divided doses) defervescence occurred, the mucosal lesions healed, and the abnormal roentgenologic findings disappeared except for a small, thin-walled, apical cavity. Meningitis appeared at the end of the second month and the patient received 32 intrathecal injections of 0.1 to 0.375 gm. of streptomycin in a total period of forty days, with no significant clinical improvement. Relapse of the pharyngeal lesions occurred during the third month of therapy and was also accompanied by a return of the miliary densities on the roentgenogram. Despite continuation of the streptomycin, the infection progressed steadily, virtually complete deafness developed, and the patient died November 12, 1946, 101 days after the start of antimicrobial therapy.

Cultures of tubercle bacilli isolated from the sputum before therapy were completely inhibited by 1.0 microgram of streptomycin per cc. of medium. On the sixty-first day, bacilli resistant to 500 micrograms per cc. were cultured from the sputum and also from the cerebrospinal fluid. Subsequent cultures isolated from the cerebrospinal fluid, however, were sensitive to 2.0 to 15 micrograms of streptomycin, but terminally, drug-resistant bacilli were also cultured from this source.

*Gross pathological findings* (Autopsy No. 12180): In the upper lobes of both lungs were

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FIG. 19. Case 5. Healing small tubercle in the brain. Several of these lesions are found in the pons. Each is composed of a mass of fibrous tissue in which are some macrophages and giant cells, but no areas of caseation.  $\times 150$ .

FIG. 20. Case 5. Encapsulated tubercle in the kidney. The caseous center is surrounded by a dense fibrous capsule. About this lesion, however, are a few small active tubercles, one of which is actually in the capsule itself.  $\times 90$ .

FIG. 21. Case 5. Healing tubercles in the liver. These are very numerous, almost giving the appearance of cirrhosis. Each is composed of fibrous tissue, macrophages, and lymphocytes.  $\times 90$ .

tuberculous cavities, the largest 3.5 cm. in diameter. There was extensive tubercle formation and areas of caseation about many of the bronchioles throughout these lobes and in areas in the lower lobes. Scattered throughout the lungs were great numbers of miliary tubercles measuring up to 3 mm. in diameter. The hilar nodes were slightly enlarged, grey-white, and firm.

Throughout the lungs and beneath the pleural surface were numerous small cysts lined by a thin smooth membrane and measuring from 2 to 15 mm. in diameter.

The posterior pharynx, the epiglottis, and the vocal cords were ulcerated. Lateral to the larynx was a small abscess cavity.

There were numerous miliary tubercles in the spleen and liver, and fewer in the kidneys and adrenals. In the ileum and cecum were areas of tuberculous ulceration. In the lymph nodes about the cecal region were some areas of caseation.

The arachnoid was moderately thickened and opaque. A few small tubercles were seen over the base of the brain. In the cerebellum was a tuberculoma 6 mm. in diameter.

*Postmortem bacteriologic examination:* Cultures of the lung grew tubercle bacilli which were resistant to more than 500 micrograms of streptomycin per cc. of medium.

*Microscopic observations:* In sections through cavities in the right upper lobe the walls consisted of a thin layer of epithelioid cells, fibroblasts, and a few giant cells, and in the caseous contents were many acid-fast organisms. In the adjacent lung tissue were tuberculous abscesses. In the lung tissue away from the cavities were numerous "soft" miliary tubercles containing many acid-fast bacilli. In addition, there were many small and large scars characteristic of healed tubercles and some scars which contained areas of tuberculous activity. None of the healed lesions contained acid-fast bacilli. In the lung parenchyma were a few thin-walled, noninfected cysts. In the pharynx, larynx, and back of the tongue were superficial and deep tuberculous ulcers containing many acid-fast bacilli.

Most of the lymph nodes contained many areas of early softening, often forming focal abscesses. In a few were small hyalinized scars. In the liver were active miliary tubercles and some focal scars. Acid-fast bacilli were seen in the tubercles with caseous centers, but not in the scars. In the spleen were many small active tubercles.

In the right anterior cerebellum was a tuberculoma composed of caseous material and containing large numbers of acid-fast bacilli. In the meninges were large caseous tubercles with poorly formed walls. Many of the small arteries showed a marked intimal fibrous proliferation.

#### *Anatomical diagnoses:*

Pulmonary tuberculosis with cavity formation.

Ulcerative tuberculosis of the larynx, pharynx, ileum, and cecum; and tuberculosis of hilar and mesenteric lymph nodes.

Generalized miliary tuberculosis with healed miliary tubercles in the liver and lungs, and caseous, soft, miliary tubercles in these and other organs.

Tuberculoma in cerebellum and advanced tuberculous meningitis with fibrous endarteritis.

An accessory diagnosis was cystic disease of the lungs.<sup>5</sup>

<sup>5</sup> The nature of the multiple cysts, without trace of inflammatory reaction in their walls, is obscure. They do not have the structure of emphysematous bullae. One of us (C. M.) regards them as probable cavities resulting from miliary tubercles. The majority interpret them as cystic disease, probably of congenital origin. To our knowledge, no other instance of this type of multiple cavitation (if it be such), showing no specific tuberculous granulation tissue, has been described in miliary tuberculosis with or without streptomycin therapy.

### Summary and Comment

A 19-year-old white female developed a diffuse pulmonary tuberculosis, tuberculous ulceration of the pharynx and epiglottis, and generalized miliary tuberculosis. Streptomycin produced clinical healing in all lesions; ultimately meningitis developed, and the lesions returned. Tubercle bacilli became markedly resistant to streptomycin *in vitro*.

At autopsy focal scars in the lungs and liver gave evidence of healing; otherwise the picture was that of progressive disease. The meningitis was advanced with marked arteritis.

*Case 7 (A.Ke.) Clinical summary:* The patient was a 63-year-old man who developed acute meningeal and miliary tuberculosis as a complication of chronic pulmonary and laryngeal disease.

Streptomycin therapy consisted of 3.0 gm. daily in divided doses by the intramuscular route and 0.1 gm. intrathecally at forty-eight hour intervals. The total period of therapy was thirty-eight days, during which 21 intrathecal treatments were given.

Clinical improvement was evident during the first week of treatment, although some signs of meningitis persisted. Improvement continued and the temperature gradually fell until the thirty-seventh day of treatment when the patient suddenly became critically ill and expired within twenty-four hours.

Cultures of tubercle bacilli isolated from sputum and cerebrospinal fluid before treatment were completely inhibited by streptomycin concentrations of 1.95 micrograms per cc. of medium.

*Gross pathological findings (Autopsy No. 12392):* The upper lobe of the right lung was replaced by fibrous tissue containing multiple small, thin-walled cavities partly filled with caseous material. In the remainder of the lungs were areas of tuberculous bronchopneumonia. Throughout the lungs were numerous 1 to 2 mm. miliary tubercles. The epiglottis and vocal cords were thickened and ulcerated.

A few miliary tubercles were seen in the liver and spleen and many focal grey-yellow areas, measuring up to 7 mm. across, in the kidneys. In the mucosal surface and involving the muscularis of the jejunum and ileum were many large (up to 3.5 cm. across), firm, grey-yellow, circumscribed areas of fibrous thickening, in the centers of which were irregular areas of ulceration.

The cerebral convolutions were slightly flattened and the arachnoid over the brain was thickened and contained a few small tubercles. The arachnoid of the spinal cord was thickened and opaque and contained many small, round, white tubercles.

*Postmortem bacteriologic examination:* Cultures of the lung and cerebrospinal fluid failed to grow tubercle bacilli. Bacilli isolated from the kidney were sensitive to less than 1.95 micrograms of streptomycin per cc. of medium. Those from the brain required between 8 and 15 micrograms of streptomycin per cc. for complete inhibition.

*Microscopic observations:* The cavities in the upper lobe of the right lung were surrounded by fibrous tissue and lined by caseous material containing many acid-fast bacilli. In the other lobes of the lungs were numerous small tubercles, with thick fibrotic walls, epithelioid cells, occasional giant cells, and central caseation containing acid-fast bacilli. Elsewhere were scattered focal scars.

In the liver were scattered fibrous nodules containing lymphocytes and macrophages. In the spleen were scattered tubercles composed of epithelioid cells, giant cells, and fibrous tissue. In the kidneys were several fibrotic tubercles.

In the ileum, in sections taken through two of the lesions observed in the gross, the submucosa was greatly thickened by masses of macrophages, lymphocytes, some polymorphonuclear leukocytes, and fibroblasts. A few tubercle bacilli were found.

Examination of the cauda equina showed perivascular fibrosis and a marked cellular exudate consisting of lymphocytes and macrophages surrounding the cord and matting the nerve roots together, with marked infiltration of the roots and some invasion of the dura and one of the posterior root ganglia. In the meninges over the brain were a few active tubercles.

*Anatomical diagnoses:*

Chronic pulmonary tuberculosis with cavitation.

Chronic ulcerative tuberculosis of the larynx and epiglottis.

Hyperplastic tuberculous enteritis, with some healing.

Miliary tuberculosis with healed and active miliary tubercles in the lungs and liver and fibroplastic tubercles in the spleen and kidneys.

Acute tuberculous meningitis and meningoradiculitis with some healing about the cauda equina.

### Summary and Comment

A 63-year-old white male with chronic pulmonary tuberculosis, generalized miliary tuberculosis, and tuberculous meningitis was treated with streptomycin for thirty-nine days. There was a transient improvement, then death. At autopsy there was no alteration of the ulcerative process in the lungs, but the disseminated lesions in the lungs showed marked fibrosis and microscopic evidence of healing, as did those in the liver and kidneys. The intestinal ulcers and the disease in the cauda equina also showed evidence of healing. Tubercle bacilli remained sensitive, except for those cultured from the brain postmortem which required 8 to 15 micrograms of streptomycin per cc. of culture medium for inhibition.

### RECAPITULATION OF HISTOLOGICAL OBSERVATIONS

#### Lungs

*Modification of the miliary tubercles:* Several types of modified miliary tubercles were observed in the lungs. The first was a focal fibrotic scar (figures 1, 2, 3, 10, 11, 14). These were observed in varying numbers in each of the seven cases of miliary tuberculosis. Some of the scars were small, at times only 3 to 5 alveolar spaces in length and 1 to 2 in width, but others were considerably larger. Each consisted of a loose network of collagen containing a few fibrocytes, macrophages, and lymphocytes, as well as some capillaries. No acid-fast bacilli could be found in sections of these scars.

In Case 1, a child of eighteen months, there were no active tubercles in the lung tissue, only scattered focal scars. In this case a roentgenogram of the chest before treatment was begun had revealed widespread miliary tuberculosis and the gastric washings had contained tubercle bacilli. With streptomycin therapy the miliary lesions in the lung disappeared completely and never recurred in the nine remaining months of life. At necropsy the lung tissue contained no visible

scars and no tubercle bacilli could be found on culture. Scattered in a uniform fashion throughout the lung substance were focal microscopic scars (figures 1, 2, 3). The conclusion of Baggenstoss, Feldman, and Hinshaw (1) that such scars result from the healing of miliary tubercles seems justified, and we have also referred to these lesions as "healed miliary tubercles." This case was the only one in which there was complete healing in the lungs.

In each of the other six cases of miliary tuberculosis treated with streptomycin, scattered scars and active miliary tubercles were found. In some cases, such as Case 2, the scars often were predominant; and in others, as Case 7, they were very few in number and healing was often less complete. In each of these cases there had been a favorable response to the drug followed by a relapse. In these six cases many of the active tubercles may have come from a second hematogenous seeding of the bacilli, but in others one could occasionally observe scars on one border of an active "soft" tubercle containing many acid-fast bacilli (figure 10). This lesion was seen occasionally in Cases 3, 6, and 7, and less frequently in Cases 2 and 4. This recurrence of an active, rapidly spreading, "soft" tubercle, containing many tubercle bacilli in what was a partially healed miliary tubercle with advanced scarring, is the second modification of the miliary tubercle which was observed.

In Case 4, where a clinical remission of two months was followed by an overwhelming infection, a third modification was observed in that the miliary tubercles in the lungs were very large, measuring as much as 3 mm. in diameter, and on microscopic examination showed a large central area of necrosis, surrounded by an incomplete ring of collagen, and outside of this another zone of necrosis (figure 13). In the areas of caseous necrosis were many acid-fast bacteria. This suggests that with the clinical relapse, which was associated with the appearance of streptomycin-resistant organisms, the infection spread outwards from the unhealed caseous center through the fibrous wall, to envelop the original tubercle.

Other modifications consisted of various exaggerations of the collagen which normally surrounds the caseous centers of miliary tubercles. Some of the miliary lesions had a very dense fibrous wall surrounding a focal area of caseation or necrosis, whereas others had only an exaggerated capsule. This suggested that the process either had persisted for a longer time than usual, or, and this seems more likely, that there was marked healing early in the course of streptomycin therapy and that the reactivation began in the central portions of the tubercles.

*Effect on tuberculous cavities:* In Case 7 chronic tuberculous cavitation was the primary disease, and in two others (Cases 3 and 6) there were cavities in the lung at autopsy. No unusual changes could be seen in the walls of these cavities.

*Other pulmonary lesions:* In Case 5 there were some healed miliary tubercles of a remarkable size (figures 16 and 17), and some very small areas of necrosis in which a few acid-fast bacilli could be seen. In the walls of the vessels were many small tubercles and multiple small thrombi, a tuberculous endoangitis

(figures 16 and 18). This case is difficult to interpret and perhaps had best be considered as a very unusual type of chronic tuberculous pneumonia, possibly arising from miliary tuberculosis. The organism recovered from the lungs after death grew very slowly as compared to those recovered from the other cases.

The peripheral primary complex was observed in the lungs in Cases 1 and 2. Both of these were young children, and in each, before the start of streptomycin therapy, a roentgenogram of the lungs showed a dense large shadow with poorly defined borders in the peripheral portions of the lungs. Calcification, if present, was poorly defined. Under treatment, these lesions appeared to become more circumscribed and calcification became evident. In the first case, at autopsy the peripheral tubercle and hilar node were composed of a mass of partially calcified caseous material surrounded by a dense wall of fibrous tissue. No giant cells or other evidence of activity could be seen, and no acid-fast bacilli were found. On the basis of the histological appearance of the lesions, one can say that the disease process was arrested. In the corresponding lesions of the second case there was a thin fibrous capsule about the partly calcified caseous material, but in it were recent areas of caseation and giant cells. No acid-fast bacilli could be seen.

### Liver

In each of the seven streptomycin-treated cases of miliary tuberculosis included in this study, focal scars were found in the liver (figures 5, 15, 21). These were slightly smaller than the usual miliary tubercle and consisted of a small mass of collagen containing a few lymphocytes and macrophages, but no giant cells or acid-fast bacilli. These scars apparently were the result of the healing of miliary tubercles in the liver, as has been previously described (1).

In Case 1 no active tubercles were found. In the other six cases, in addition to the scars, there were some active miliary tubercles in the liver. In Case 5 these scars and active foci were very abundant (figure 21).

### Spleen

The spleen proved to be a difficult organ in which to identify the scars of healed miliary tubercles. In Case 1 many focal scars were found in the lungs and liver, and it seemed likely that similar scars would be found in the spleen; yet none were identified. In Case 2, however, (figure 9) and in Case 5 some rather loose areas of scarring were seen in the spleen, and it seemed likely that these were healed miliary tubercles. Similar lesions were observed by Baggenstoss, Feldman, and Hinshaw (1).

In all cases save Case 1 there were some active miliary tubercles in the spleen.

### Lymph Nodes

The decrease in the size of tuberculous lymph nodes during therapy with streptomycin may be rapid; following this, the disease may not recur, or, at about the same time as the organisms evidence resistance to the drug, the nodes may rapidly enlarge and the disease progress as before the initiation of therapy (2).

In Cases 1 and 2 of this series, both infants of about two years of age with tuberculosis of lymph nodes, there was a dramatic clinical response to streptomycin therapy; the enlarged lymph nodes rapidly decreased in size and enlargement did not recur. At autopsy in Case 1 the tracheobronchial lymph nodes contained partially calcified caseous material surrounded by a dense fibrous capsule. There was no histologic evidence of activity, and acid-fast stains revealed no bacilli.

In the second case, although there was calcification of some of the caseous material in the lymph nodes, many small areas of recent necrosis and many small tubercles could be seen, suggesting activity, although no acid-fast bacilli could be demonstrated. Had this infant lived longer, it is possible that the lymph node tuberculosis would have recurred.

In Cases 3, 4 and 6 there had been extensive tuberculosis of lymph nodes during life which had regressed for a time during the streptomycin therapy, only to recur. In some of the lymph nodes of these patients focal scars were seen, but in most there was only a mass of recent caseous material containing many bacilli. As there was such extensive disease of these nodes at autopsy, it is probable that evidence of healing may have been obscured or obliterated.

#### Gastro-Intestinal Tract

In Cases 3, 4, and 6 typical tuberculous ulcers were found in the intestinal tract, and acid-fast bacilli were easily identified in these lesions. In only Case 7 was there marked healing in the ulcers, the base of the ulcers being composed of fibrous tissue containing many macrophages and a few polymorphonuclear leukocytes. No tubercles were seen, but a few acid-fast bacilli were identified in this mass of inflammatory tissue.

#### Kidney

In general the kidneys were unremarkable, but in Case 5 changes were observed. This man had had a nephrectomy for renal tuberculosis about two years before his death from generalized miliary tuberculosis, and during his streptomycin therapy developed evidence of renal damage, as indicated by decreased renal function tests and elevated blood urea nitrogen. He died with uremia. The remaining kidney contained many small rounded scars having the appearance of healed small tubercles, and some diffuse fibrosis of the parenchyma. There were also a few recent caseous miliary tubercles. In the organ were also a few larger tubercles with a caseous center surrounded by a thick fibrous capsule (figure 20). There was also degeneration of the tubular epithelium and focal areas of calcification within the tubules. To interpret these tubular changes as related to streptomycin therapy is difficult in view of the widespread renal tuberculosis.

#### Other Organs

Although there was clinical evidence of healing of tuberculosis of the upper respiratory tract in Case 6, the recurrence of the process may have obliterated



any evidence of healing, and the tuberculous ulcers seen at autopsy were recent and active. No healed tubercles could be identified in the bone marrow or adrenals.

### Central Nervous System

*Meninges:* In Case 3, a child of 11 years whose visceral tuberculosis responded poorly to the streptomycin therapy, autopsy showed a slight fibrous thickening of the arachnoid (figure 12) in which there were a few small and large mononuclear cells and some poorly formed tubercles without caseous centers. There was also a slight ependymitis. These findings suggest that a slight chronic meningitis persisted. The clinical history indicates that this child had had a minimal tuberculous meningitis two months before death, and tubercle bacilli were cultured from the cerebrospinal fluid before the intrathecal streptomycin therapy was begun.

In Case 1 the meningitis was of a very chronic nature and was terminated by internal hydrocephalus. This child had the meningeal disease for at least eight months, a much longer period of time than Case 3, and was given two courses of intrathecal streptomycin. For the last fifty-six days of life the cerebrospinal fluid contained no tubercle bacilli on repeated examinations. At autopsy there was a marked chronic healing tuberculous meningitis (figure 4) with fibrous endarteritis; tubercle bacilli could not be demonstrated by culture or by acid-fast stain. Nevertheless, a few tubercles with caseous centers, but no giant cells or acid-fast bacilli, were found in the choroid plexus (figure 6). It is difficult to be certain of the degree of activity of the disease in these lesions.

A marked chronic but active tuberculous meningitis was found in Case 2 (figure 7), and the massive fibrosis and vascular intimal proliferation (figure 8) reflected the long-standing disease process (seven and one-half months). A few acid-fast bacilli were found in the meninges, and postmortem cultures yielded bacilli sensitive *in vitro* to streptomycin.

In one case (Case 7), an acute tuberculous meningitis was found in association with a meningoradiculitis, showing some evidence of healing in the cauda equina. Tubercle bacilli recovered from the brain postmortem showed moderate resistance to streptomycin.

An advanced meningitis, associated with a tuberculoma of the cerebellum and with some fibrous endarteritis, was present in Case 6. The meningitis in this case showed no evidence of healing. The bacilli varied somewhat in sensitivity, but eventually became resistant *in vitro*.

*Brain:* In Case 5 healing tubercles were found in the brain (figure 19). These were seen in the pons and consisted of fibrous nodules, in the centers of which were a few giant cells, monocytes, and lymphocytes. No acid-fast bacilli or areas of caseation were found. In Case 6 there was a tuberculoma in the cerebellum, which showed no evidence of healing.

A preliminary report of the study of the changes seen in the eighth cranial nuclei has already been published (5), and it may be stated here that degeneration of the neurones in the ventral cochlear nuclei was seen in all cases in which there

was clinical evidence of deafness and where these structures were examined (Cases 1, 2, 3, 4, 5, and 6). There was also degeneration of the neurones in the inferior vestibular nuclei in Cases 3 and 4.

#### DISCUSSION

In the seven cases of miliary tuberculosis treated with streptomycin which have come to autopsy, there was evidence of healing in all. In each of these the most impressive evidence of healing was found in the miliary tubercles of the lungs and liver, and in some instances in the spleen, although even in these tissues healing was often incomplete or transitory. Similar observations have been made by Baggenstoss, Feldman, and Hinshaw (1), who concluded that the best evidence of healing occurred in the comparatively minute miliary lesions.

In only one case (Case 5) was there histopathologic evidence of healing of miliary tubercles in the kidney, but this was not complete.

There is little doubt that healing of occasional miliary tubercles occurs at times in viscera such as the liver and spleen, and, indeed, there are many reports of healing in miliary tuberculosis (see discussion in Reference (1)). It is likely, however, that the healing of a widespread dense seeding of miliary tubercles is rare, as is indicated by the infrequency of such reports as compared to the abundance of the disease itself. It is evident also that, whereas healing of a few scattered miliary tubercles may occur, it is unusual to see evidence of healing in the usual fatal case of the generalized miliary disease at autopsy. In a review of 20 such cases previously autopsied in this service, it was not possible to find evidence of healing such as is described in those cases treated with streptomycin in a single instance) or, as a matter of fact, in a single tubercle.

In some cases (Cases 3, 4, and 6) there was excellent clinical evidence of the temporary regression of the tuberculous process in lymph nodes. In each of these the disease recurred, but there was no evidence aside from a few focal scars, which may be found in many lymph nodes draining a tuberculous process, of the massive healing process which presumably occurred. It is even difficult to say if the healing and calcification of the primary complex observed in Cases 1 and 2 is unusual. Clinical observations suggest that this process occurred more rapidly than is customary without streptomycin, but exact evaluation is difficult. The pathologic examination revealed nothing unusual in the process of healing of the primary complex.

The brain and leptomeninges should be considered separately from the visceral lesions of tuberculosis. With intrathecal administration of streptomycin, it is possible to achieve far higher concentrations of the drug in the cerebrospinal fluid than in the blood, and it might be expected that organisms in the meninges could thus be subjected to far higher concentrations of the drug than those in visceral lesions. Unfortunately, the flow of cerebrospinal fluid is from the ventricles outward, and the choroid plexus, the ventricular system, as well as the depths of the cortical sulci may be expected to be subjected to much lower concentrations of streptomycin than the remainder of the meninges. It has been shown (6, 1) that only low concentrations of streptomycin are attained in the

brain substance or cerebrospinal fluid following intramuscular administration. Baggenstoss, Feldman, and Hinshaw (1) believe that this failure of streptomycin to penetrate the substance of the brain in appreciable amounts may, at times, account for the presence of progressive lesions of the brain in absence of tuberculous meningitis. The healing tubercles observed in the pons (Case 5), however, seem contrary to this belief.

In the present series there were six cases with tuberculous meningitis. Of these, two cases (Cases 1 and 2) showed marked early clinical improvement, but the reduction of the cerebrospinal fluid sugar at the time of otherwise complete clinical remission, in spite of negative culture, strongly suggested that the tuberculous meningitis had persisted throughout the prolonged course of seven and one-half to eight months. This was also borne out by the marked degree of fibrosis of the meninges with internal hydrocephalus observed at autopsy. It was remarkable that after such a long course of treatment the last bacilli isolated were still sensitive to streptomycin. Case 3 was quite similar to these two in early clinical response, and death from recurrent visceral miliary tuberculosis afforded an opportunity to observe the meningitis after two months of treatment. The pia-arachnoid over the base of the brain showed slight fibrosis and lymphocytic inflammation. The presence of a few areas of activity, consisting of small groups of epithelioid cells and rare giant cells, suggests that the meningitis might subsequently have relapsed.

The peculiar fibrosis matting the nerves of the cauda equina together in Case 7 is indicative of some healing. Although no modification of the tuberculous meningitis was demonstrable in Case 6, the isolation of tubercle bacilli from the cerebrospinal fluid on the twenty-sixth day, with no further signs of meningitis until the fifty-eighth day, is remarkable and indicative of the long incubation period which may be required in some cases.

As the clinical diagnosis of tuberculous meningitis in Case 4 was in doubt, and the meningitis found postmortem seemed acute, certainly not four months old, and as the patient was not treated terminally with intrathecal streptomycin, this case was not included as one of streptomycin-treated tuberculous meningitis.

The presence of a chronic arteritis in these cases of tuberculous meningitis was also of interest. This was most marked in the meninges of Case 2, where there was great fibrous thickening of the intima, producing considerable narrowing of the lumen; less marked changes were observed in the meninges of Cases 1 and 6. These changes were similar to those described in pneumococcic meningitis treated with sulfonamides (7). Whether these changes were the result of healing of an acute tuberculous arteritis, or were produced by the surrounding chronic inflammation, is not known.

Although an exact correlation between the clinical, pathological, and bacteriological findings is difficult, the studies on what is usually called the "streptomycin-resistance" of the tubercle bacilli are of interest. In Cases 1 and 2, where the early clinical responses seemed good and where no drug-resistant bacilli appeared, there was evidence at autopsy of marked healing with little or no acute tuberculous activity. In the three cases (Cases 3, 4, and 6) where favorable

early clinical responses were evident (in Case 4 being almost as good as in Cases 1 and 2), but where overwhelming relapses subsequently occurred, drug-resistant tubercle bacilli appeared. In the latter cases the autopsies showed considerable tuberculous activity in addition to healing. Cases 5 and 7 cannot be considered from this standpoint because in one instance proper studies of the drug resistance of the bacilli could not be made; and in the other, death was inexplicably sudden.

#### SUMMARY

The modifications of tuberculous lesions seen at autopsy in seven patients treated with streptomycin have been described. Each of the cases had generalized miliary tuberculosis and had shown from a slight to a marked clinical improvement during the treatment with the drug. In each there was pathologic evidence of healing of the miliary tubercles in the form of focal scars in the lungs and liver, and occasionally in other viscera.

In two cases, both young children, the generalized miliary disease did not recur clinically. In one there was no evidence of active disease in the lungs or lymph nodes at death; in the other there was slight activity. Both died of chronic meningitis.

Of the five cases with tuberculous meningitis treated by intrathecal streptomycin, three showed marked modification. A marked fibrous proliferation of the intima of large meningeal arteries was present in two of these in which an early favorable clinical response was followed by fibrous thickening of the leptomeninges and death from hydrocephalus. In one case without meningitis, several healing tubercles were seen within the pons.

In the three cases where the tubercle bacilli manifested resistance to streptomycin during therapy, the disease process was quite active at the time of death; whereas, in the two cases where no resistance appeared, there was little or no evidence of activity.

#### SUMARIO

##### *Modificaciones de las Lesiones Tuberculosas en los Enfermos Tratados con Estreptomicina*

Describense las modificaciones de las lesiones tuberculosas observadas al hacer la autopsia en siete enfermos tratados con estreptomicina. Todos los casos eran de granulía y habían revelado de leve a pronunciada mejoría clínica durante el tratamiento con la droga. En todos había signos patológicos de cicatrización de los tubérculos miliares en forma de cicatrices focales en los pulmones e hígado, y en ocasiones en otras vísceras.

En dos casos, ambos en niños pequeños, la afección visceral no recurrió clínicamente. En uno no había signos de enfermedad activa en los pulmones o ganglios linfáticos al tener lugar la muerte; en el otro la actividad era leve. Ambos murieron de meningitis crónica.

De los cinco casos de meningitis tuberculosa tratados con estreptomicina por vía intratecal, tres mostraban modificación pronunciada. Existía marcada

proliferación fibrosa de la íntima de las grandes arterias meníngeas en tres casos de meningitis tuberculosa, dos de ellos con la forma crónica de la enfermedad, y el tercero, el único caso sin modificación. En un caso sin meningitis, observáronse varios tubérculos en vías de cicatrización en el puente de Varolio.

En los tres casos en los que los bacilos tuberculosos manifestaron resistencia a la estreptomycin durante el tratamiento, el proceso patológico se hallaba bastante activo en el momento de la muerte, en tanto que, en los dos casos en que no apareció resistencia, los signos de actividad eran pocos o nulos.

#### *Acknowledgment*

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# ANATOMIC CHANGE IN TUBERCULOSIS FOLLOWING STREPTOMYCIN THERAPY<sup>1,2</sup>

OSCAR AUERBACH AND GRANT N. STEMMERMAN

## INTRODUCTION

The use of streptomycin in the treatment of tuberculosis has now reached the point where the accumulation of surgical and necropsy material is sufficient to enable the pathologist to assay its effects upon the disease. The authors wish to present observations in seven autopsy cases. It should be emphasized that, although this is but a preliminary report, the changes to be described are so constant and so striking as to merit their publication at this time.

These necropsy cases include all patients who had died after receiving streptomycin at the Halloran Veterans Administration Hospital regardless of the length of their course or the interval between cessation of treatment and death. The sensitivity of recoverable organisms to streptomycin has been recorded wherever possible and it is believed that this must be considered in weighing the effect of the drug in individual cases. The clinical response to the treatment will not be mentioned in great detail since previous articles seem ample to cover this realm of observation. Rather it is intended to delineate the morphologic changes and speculate upon the effects these changes may have upon the course of the disease.

It is difficult to assess the effects of streptomycin when so few cases are available for study. The size of lesions and the extent of their distribution vary considerably, and each case must be compared with the average untreated case of similar type. The age and race of the patient, the duration of illness, and the manner in which he had been treated before streptomycin therapy are the best yardsticks with which to measure each case. The weight of a considerable past experience must be brought to bear in order properly to evaluate streptomycin therapy. The writers are well aware that any individual will vary considerably from the average, but believe that at least moderately accurate assumptions may be based on this approach.

## CASE REPORTS

*Case 1:* S. M., a 52-year-old white man, was well until August 1945, at which time he developed a bilateral pleurisy. Aspirated chest fluid and bronchial aspirations were negative for acid-fast bacilli. After recovery he was followed at a chest clinic and remained well until October 1946, at which time he complained of low back pain and rapid loss of weight. He was admitted to another hospital where his sputum was now positive for tubercle bacilli, and roentgenograms of the chest revealed miliary type lesions throughout both lungs. Roentgenographic studies also revealed destructive changes in the third and

<sup>1</sup> Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

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fourth lumbar vertebrae. Streptomycin therapy was begun on May 23, 1947, and the patient was transferred to this hospital. The treatment was continued until July 14, 1947. The patient was given 2.0 grams of the drug daily for a total of 104 grams. Treatment was stopped because of the development of a rhythmic Parkinsonian type tremor involving his arms and legs. During this period temperature climbed to 102°F. A lumbar puncture at this time showed no abnormal findings and it was presumed that his tremor was due either to streptomycin sensitivity or to tuberculous destruction of the brain parenchyma. His course continued downhill and he became comatose and died on August 5, 1947.

*Pertinent necropsy findings:* The pleurae were thickened and the pleural spaces were completely obliterated. Scattered throughout all lobes of the lungs were numerous elevated, firm, grey foci measuring less than one mm. in diameter. A collection of round, elevated, yellow foci was present 1.2 cm. from the apex of the upper lobe of the left lung. These were surrounded by thick grey capsules. Similar lesions were present in the upper lobe of the right lung, but these contained stony hard material within them.

Present within the liver were numerous sharply defined yellow foci measuring less than one mm. in diameter.

The prostate contained within it a large, poorly circumscribed, yellow focus. This lesion had a semiliquid consistency in its central aspects.

Hemisection of the spinal column revealed a defect which extended from the antero-inferior portion of the third lumbar vertebral body to the antero-superior portion of the fourth lumbar vertebral body. The defect was filled with a gelatinous yellow material. The posterior portions of the involved vertebral bodies were firm and yellow. The anterior longitudinal ligament was destroyed in this region. The vertebral bodies were surrounded by bilateral paravertebral abscesses which were continuous with large psoas abscesses.

Five mm. coronal sections of the brain revealed the cerebral hemispheres, cerebellum, pons and medulla oblongata to contain yellow foci varying from 7 mm. to 1.8 cm. in diameter. Many of these were softened centrally. One of these in the cerebellum was directly continuous with the overlying meninges. On the meningeal surfaces of the brain in the region of the cerebello-pontine angle and in the postero-inferior aspects of the cerebellum were numerous elevated, oval and round, yellow foci measuring from 1 to 5 mm. in diameter. Similar foci were also present in the meninges covering the spinal cord.

*Histopathology:* Present throughout the lung parenchyma were numerous small, round foci composed of loose connective tissue containing a few epithelioid cells. Similar foci were also present in the submucosal portions of the pulmonary bronchi. Larger encapsulated, caseous lesions were also present.

Present in the kidneys, spleen and liver were numerous oval and round foci. These were composed of loosely and concentrically arranged epithelioid cells, fibroblasts, collagen fibrils and an occasional Langhans giant cell. Those in the liver and spleen enclosed a pink caseous center.

The anterior portions of the third and fourth lumbar vertebrae were completely destroyed and replaced by pink-blue caseous material. Beyond this was a typical tuberculous granulation tissue which extended into the posterior portions of the vertebrae where it enclosed smaller caseous areas.

The caseous focus in the prostate was surrounded by tuberculous granulation tissue. Intact glands persisted within this zone.

The foci in the brain were composed centrally of caseous material surrounded by a vascular granulation tissue composed of dilated capillaries, glial cells, polymorphonuclear

leucocytes, and epithelioid cells. In the cerebellum the zone of caseation extended into the meninges. Scattered throughout the meninges were numerous small foci. These had a pink caseous center and were surrounded by lymphocytes, plasma cells, polymorphonuclear leucocytes and epithelioid cells.

*Case 2:* B. O., a 19-year-old Negro man, had negative chest films on March 7, 1944, and April 2, 1945. On June 16, 1946, a routine chest roentgenogram revealed an infiltrate in the first and third right anterior interspaces. The patient was asymptomatic at this time. A tentative diagnosis of primary atypical pneumonia was discarded when, after two months, he developed a cough and fever, and sputum examination revealed the presence of acid-fast bacilli. In October 1946 several cavities were noted in the right upper lung fields and the patient began to lose weight. Roentgenograms in February 1947 revealed a spread of the disease to the lower lobe on the right and to both upper and lower lobes on the left. On March 1, 1947, the patient was placed on streptomycin, 2.0 grams daily. His cough decreased in amount and some improvement was noted on roentgenographic examination of the chest. He continued to lose weight, however, and his temperature rose daily to 102°-103°F. The drug was stopped on July 3, 1947. During the treatment his sputum always contained acid-fast bacilli and at the close of treatment these organisms were resistant to 125 micrograms of the drug per cc. of medium. The patient's course continued downhill and he died on October 3, 1947.

*Pertinent necropsy findings:* Present in the upper lobe of the left lung were numerous cavities which varied from 5 mm. to 2.5 cm. in diameter. These had irregular outlines. The cavity walls varied from less than one to one mm. in thickness. Scattered throughout the remaining portions of the parenchyma were numerous yellow foci varying from 2 mm. to 1.5 cm. in diameter. The larger of these foci had a lobular configuration. The lower lobe of the left lung was similar in appearance to that just described. The upper lobe of the right lung was almost entirely occupied by a system of interlocking cavities, the walls of which varied from less than one mm. to 3 mm. in thickness. What remained of the lobe was occupied by numerous yellow foci which had a lobular configuration. The middle and lower lobes of the right lung were similar in appearance to the left lung. The visceral and parietal pleurae over all portions of both lungs were thickened and the pleural space was obliterated. Contained within the right inferior tracheobronchial lymph node was a yellow stony hard focus which measured one mm. in diameter. The mucosa over the epiglottis was pink granular in appearance.

*Histopathology:* The cavity in the upper lobe of the right lung was lined by a layer of caseous material. Beyond this was a pyogenic membrane, and a vascular granulation tissue composed of epithelioid cells, giant cells, fibroblasts, collagenous fibers, and dilated capillaries. The outer portions of the cavity wall were composed of interlacing bands of collagenous connective tissue within which were compressed and distorted alveoli. Miliary foci, acinous nodose foci and extensive areas of caseous lobular pneumonia were present in all portions of the remaining lung parenchyma. The miliary foci enclosed small central zones of caseation. The areas of caseous pneumonia showed little tendency to organization in their peripheral portions. An extensive perifocal reaction surrounded all these lesions. In addition to the encapsulated caseous foci already described in the gross, there were numerous small oval and round miliary foci within the tracheobronchial lymph nodes. The central portions of these foci had a pink granular necrotic appearance.

Present within the submucosa of the larynx, kidney, liver, spleen, and bone marrow of the lumbar vertebrae, were numerous small, round, miliary foci similar to those already described in the lung and lymph nodes.

*Case 3:* J. M., a 53-year-old white man, was well until the autumn of 1945, at which time



he developed a productive cough. In the following twelve months he lost sixty pounds in weight. In February 1947 he was admitted to another hospital where a diagnosis of tuberculosis was made on the basis of a positive sputum. Roentgenographic examination at this time revealed an infiltration throughout the right lung and within the upper half of the left lung field. Numerous small cavities were present throughout the right upper lobe. The patient's temperature varied from normal to 101°F. He was started on streptomycin, 2.0 grams daily, May 14, 1947. His cough and sputum decreased and he began to gain weight. His temperature returned to normal. There was, however, little change in the roentgenographic appearance of his pulmonary lesion and his sputum persistently contained acid-fast bacilli. He was transferred to this hospital on June 24, 1947. The streptomycin was discontinued after 120 days of treatment on August 19, 1947. Except for a considerable dyspnea, the patient was asymptomatic. He died in his sleep on November 7, 1947.

*Pertinent necropsy findings:* The left upper lobe of the lung contained in its posterolateral aspect a cavity which measured 3.5 by 4.5 cm. and which was lined by a dirty grey membrane. The cavity wall measured 3 mm. in thickness and fused with the lateral pleura. Also present in this lobe were numerous encapsulated, yellow foci measuring from 2 mm. to 1.5 cm. in diameter. Many of these contained stony hard material in their capsular portions. Others were liquefied centrally. Traversing the lung parenchyma were broad bands of tough grey tissue. The lower lobe of the left lung contained many cavities within its upper half. These varied from 1.5 to 4.5 cm. in diameter. The cavities were similar in appearance to those just described in the upper lobe. The remaining portion of the lobe was occupied by lesions similar to those in the upper lobe.

The right upper and middle lobes were greatly contracted. The former contained a large thick-walled cavity within it. The remaining lung parenchyma was firm, inelastic, and contained numerous encapsulated foci within it. The middle lobe of the right lung contained numerous encapsulated yellow foci within it also, as did the lower lobe. Also present within the latter lobes were two small thick-walled cavities.

Present within the right inferior tracheobronchial lymph node were several stony hard, yellow foci which varied from 1 to 5 mm. in thickness.

The heart weighed 500 grams, and scattered throughout the myocardium of the left ventricle were numerous grey bands of tissue. These were also present in the interventricular septum where they occupied a patch-like area measuring 4 cm. in diameter. The lumina of all the coronary arteries were narrowed by arteriosclerotic plaques and that of the left circumflex artery was only slit-like and filled with a firmly attached thrombus.

*Histopathology:* Microscopic examination of the cavities in all lobes revealed them to be lined by a layer of caseous debris, beyond which was a typical tuberculous granulation tissue. The outer portions of the cavity wall were composed of wide interlacing bundles of connective tissue. The encapsulated foci described grossly were not unlike those found in any untreated case of pulmonary tuberculosis. In addition to the stony hard focus already described grossly, the tracheobronchial lymph nodes contained within them many contiguously arranged miliary foci composed of epithelioid cells, giant cells, fibroblasts, and collagenous fibers, the last named predominating.

*Case 4:* S. B., a 27-year-old white man, was last well in October 1943, when as a prisoner of war in Burma he developed a cough and hemoptysis. His disease was not diagnosed or treated until December 1946, at which time he had returned to the United States. Chest roentgenograms at that time revealed a cavity in the left upper lobe and the patient's sputum contained acid-fast bacilli. A two-stage thoracoplasty was instituted, but after this treatment his vital capacity fell to 9 per cent of normal and the patient developed

considerable wheezing, a hacking cough, and roentgenographic evidence of a spread to the contralateral lung. Streptomycin therapy, 2.0 grams daily, was begun on April 8, 1947. After treatment there was marked subjective improvement, his sputum decreased in amount, and he gained in weight. The drug treatment was continued for 120 days, but at the close of treatment his sputum continued to contain acid-fast bacilli. His vital capacity was found to be 26 per cent of normal and pulmonary function studies revealed his oxygen diffusion to be good, whereas his ventilation was at the lower limits of normal. In view of these findings it was decided to do a left pneumonectomy to eradicate what was thought to be a patent cavity in the left lung. This was done on January 8, 1948, after the patient had been prepared with daily 1.0 gram doses of streptomycin for thirty-one day. The operation was a difficult one and the patient died five days later in what was described as respiratory failure.

*Pertinent necropsy findings:* The excised lung was shrunken, and the interlobar fissures were obliterated. The parenchyma consisted of a mass of tough, grey tissue within which no alveoli could be discerned. The bronchi throughout the lung were lined by a grey granular mucosa.

The upper lobe of the right lung contained within it occasional encapsulated, calcified yellow foci in its superolateral aspects. The intervening portions of the lobe were well aerated. The middle and lower lobes of the right lung were nonaerated and had a red granular appearance.

*Histopathology:* Microscopic examination of the excised lung revealed only occasional alveoli within the mass of connective tissue which constituted the bulk of the lung. This tissue contained occasional small, encapsulated, caseous foci within it. Scattered throughout the submucosa of the bronchi were numerous small oval foci composed of epithelioid cells, giant cells, fibroblasts and collagenous fibers. The continuity of the mucosa of a lower lobe bronchus was interrupted so that an ulcer had been formed. This was lined by a mass of caseous material which protruded into the lumen of the bronchus. Beyond this was a tuberculous granulation tissue. The lower and middle lobes of the contralateral lung were involved in an extensive bronchopneumonia.

Present in the left and right inferior tracheobronchial lymph nodes were numerous small oval and round, miliary foci composed of epithelioid cells, giant cells, fibroblasts, and collagenous fibers, with the last named predominating. Also present were small focal collections of hyaline connective tissue.

*Case 5:* G. S., a twenty-one year old Negro man, first became ill in February 1946, at which time he was admitted to a naval hospital. Tuberculosis was suspected and established on the basis of sputum examinations and roentgenograms which revealed a cavity in the upper lobe of the right lung. A pneumothorax was attempted and abandoned. Phrenic crush did not decrease the size of the cavity. The patient developed a locally tender right lower quadrant in August 1946, and in November 1946 diarrhea appeared. The patient lost twelve pounds in weight from January 1, 1947, to May 1947. For these reasons streptomycin therapy was instituted on May 27, 1947. He was given 1.5 grams per day for 120 days. The patient was transferred to this hospital on June 24, 1947. His temperature, which had been consistently febrile, returned to normal and during July and August 1947 his sputum was negative for acid-fast bacilli. Streptomycin treatment was concluded on August 24, 1948. His sputum thereafter always contained acid-fast bacilli. Because of this and in view of the large right-sided cavity it was decided to perform a right pneumonectomy. The patient was again placed on streptomycin on January 2, 1948 in a dosage of 1.0 gram per day. At this time his infecting organisms were sensitive to 5.0 micrograms of streptomycin per cc. of medium. The operation was

performed on February 12, 1948. During the operation, the patient's heart ceased to beat and artificial stimulation could not restore its normal rhythm.

*Pertinent necropsy findings:* Gross examination of the right lung revealed a large cavity 2 cm. from the apex of the upper lobe of the lung. This occupied much of the upper third of the lobe. The cavity wall measured 3 mm. in thickness and fused with the lateral pleura. The lower and middle lobes of the right lung and the remaining portions of the upper lobe contained within them numerous elevated yellow foci which varied from 2 mm. to 1 cm. in diameter. These foci had the scalloped periphery which is the hallmark of acinous nodose lesions. Also present within the lower lobe of the lung were numerous encapsulated yellow foci varying from 2 mm. to 1 cm. in diameter. Encapsulated caseous foci and acinous nodose foci were also present in the left lung, and in the lower lobe they contained white stony hard material within them.

*Histopathology:* The large cavity in the right lung was lined by a layer of caseous debris. Its inner aspects were formed of a highly cellular tuberculous granulation tissue. The outer portions of the cavity wall were composed of interlacing bundles of collagenous connective tissue. Study of the acinous nodose lesions revealed an extremely interesting phenomenon. The central portions of the lesions had the pink granular appearance of caseation. The outer portions of the lesions were composed of epithelioid cells, giant cells, fibroblasts, and collagenous fibers. The periphery of the foci was sharply demarcated from the adjacent lung parenchyma. The alveoli in this zone were empty of any of the perifocal inflammation which is usually seen in this type of lesion in untreated cases.

Microscopic examination of the bronchus draining the large cavity in the upper lobe of the right lung revealed numerous small oval and round foci many of which had a caseous center. Their outer aspects were composed of epithelioid cells, giant cells, fibroblasts, and collagenous fibers. Similar foci were also present in the hilar lymph nodes on the right side, but in this situation they contained no central zone of caseation.

*Case 6:* A. B., a 48-year-old Negro man, was well until June 1947, at which time a routine chest film revealed dense infiltration in both mid lung fields. Nodular densities were present in the lower third of the left lung, and there were peripheral infiltrations in the right upper lung field. His sputum was positive for acid-fast bacilli. He entered another hospital at that time and was treated conservatively. On July 18, 1947, he was transferred to our hospital. On admission he ran a febrile course, with afternoon rises up to 101°F. Streptomycin therapy was begun September 17, 1947, at a dosage of 1.0 gram daily. This was continued until January 17, 1948. During the period of treatment his weight increased and during December and the first three weeks of January his temperature was normal. His sputum, however, was consistently positive for acid-fast bacilli.

In the last week of January the patient's temperature again became febrile and the patient became dyspneic. As the patient's infecting organisms were still sensitive to 2.5 micrograms of streptomycin per cc., it was decided to reinstitute this therapy. This was done on February 4, 1948, but did not prevent the continued downhill course. The patient died on February 6, 1948.

*Pertinent necropsy findings:* The upper lobe of the left lung contained a cavity within its inferolateral aspects which measured 2.7 cm. in diameter. The cavity wall measured 1 mm. in thickness and was lined by a smooth grey membrane. The cavity communicated with an upper lobe bronchus and with a large cavity in the lower lobe of the lung. Scattered throughout the remaining parenchyma of the lung were numerous yellow foci varying from 3 mm. to 1 cm. in diameter. The larger of these were contiguously arranged, had a lobular configuration, and were surrounded by thick grey capsules. The smaller foci had a scalloped periphery. The upper third of the lower lobe of the left lung was oc-

cupied by a system of interlocking cavities. The cavity wall was lined by a dirty grey membrane and measured 3 mm. in thickness. Scattered throughout the remaining portions of the lobe were numerous acinous nodose foci and areas of encapsulated, caseous lobular pneumonia. One of the latter lesions occupied the whole of the inferomedial segment of the lobe. The upper, middle and lower lobes of the right lung contained within them numerous acinous nodose foci and areas of encapsulated caseous lobular pneumonia. In addition, the lower lobe also contained a cavity within it similar to those in the contralateral lung. The right and left superior tracheobronchial lymph nodes contained numerous small encapsulated chalky white foci within them. Similar lesions were also present in the mesenteric nodes.

*Histopathology:* Microscopic examination of the cavities described grossly revealed them to be lined by considerable caseous debris. Beyond this was a narrow vascular granulation tissue in which cellular elements were scarce. Epithelioid cells were few. The areas of caseous lobular pneumonia had an extremely pleomorphic appearance. In some portions the alveolar spaces were filled with polymorphonuclear leucocytes, alveolar phagocytes, giant cells, fibrin, and pyknotic nuclei. In other areas the whole lung parenchyma had a pink granular appearance and the central aspects of some of these zones were liquefied. In still other regions the alveolar exudate contained many fibroblasts and collagenous fibers within it. As in the previous case, the acinous nodose lesions were quite free of perifocal inflammation. The encapsulated lesions in the tracheobronchial lymph nodes were found to have numerous purple granular calcium deposits within them. Similar foci were also present in the mesenteric nodes, but, in addition, there were found numerous round miliary foci. A few of these had small caseous centers. Their outer portions were composed of epithelioid cells, fibroblasts, and collagenous fibers. A single fresh miliary focus was found within the spleen. This had a large caseous center and a narrow outer rim of epithelioid cells and polymorphonuclear leucocytes.

*Case 7:* G. M., a 33-year-old white man, was last well in October 1945, at which time he complained of weakness, general malaise and a productive cough. Roentgenographic examination at this time revealed an infiltrate in the upper lobe of his right lung. Acid-fast bacilli were present in the sputum. He was admitted to another hospital where a right pneumothorax was attempted in November 1945. This was abandoned because of the development of fluid in January 1946. The patient's temperature fluctuated from 99°F. to 100°F., he developed anorexia, and began to lose weight rapidly. Cultures of the pleural fluid revealed the presence of tubercle bacilli. For all these reasons streptomycin therapy in a dosage of 1.8 grams per day was instituted on August 9, 1946, and continued for 210 days. At the end of treatment the infecting organisms were resistant to 500 micrograms of the drug per cc. During and after treatment, the patient's sputum varied from Gaffky III to VI on plain smear and his temperature continued elevated. Subsequent roentgenographic studies recorded the appearance of cavities in all lobes of the lungs. The patient was transferred to our hospital in June 1947 and treated conservatively. His gradual downward progression continued until death intervened on March 9, 1948.

*Pertinent necropsy findings:* Large, thick-walled cavities, acinous nodose foci, and encapsulated caseous foci were present in all lobes of the lungs. The pleurae over the right lung were greatly thickened and the pleural space was obliterated in all but the anterior aspects where it was filled with yellow cheesy material. The pleural space in this region communicated freely with a cavity in the middle lobe of the lung. A deep-seated ulcer was present on the left vocal cord. This measured 2 cm. in diameter, had sharply demarcated edges, and a grey granular base. Present throughout the ileum and the large

intestine were numerous shallow ulcerations of the mucosa. These had a bright red base and irregular yellow-gray edges.

*Histopathology:* None of the lesions in the lungs or larynx was different from those in comparable untreated cases. The intestinal lesions were extremely fresh and extended for only a short distance into the lamina propria of the gut. Present throughout the tracheobronchial lymph nodes were numerous small, oval and round miliary foci, some of which had a small caseous center.

#### DISCUSSION

*Perifocal reaction:* The most readily observed change which streptomycin effects is to reduce perifocal reaction in the lung to a minimum. The lung parenchyma surrounding recent tuberculous lesions in the untreated case is usually packed with alveolar phagocytes, serum, and red blood cells. The extent of the alveolar filling process varies greatly, but generally it parallels in extent the tuberculous process which it surrounds. With healing, the outer portions of this perifocal reaction are expectorated or absorbed. That portion of the perifocal reaction which is not cleared from the alveoli becomes organized into loose connective tissue with a destruction of the alveolar septa. In encapsulated caseous foci this forms the outer loose connective tissue capsule, the nonspecific capsule. These areas of connective tissue extend into the surrounding lung parenchyma and account for much of the pulmonary fibrosis in chronic pulmonary tuberculosis. Contraction of this connective tissue stretches and tears the surrounding alveolar septa, resulting in a perifocal emphysema. Both the fibrosis and emphysema decrease the amount of functioning lung parenchyma.

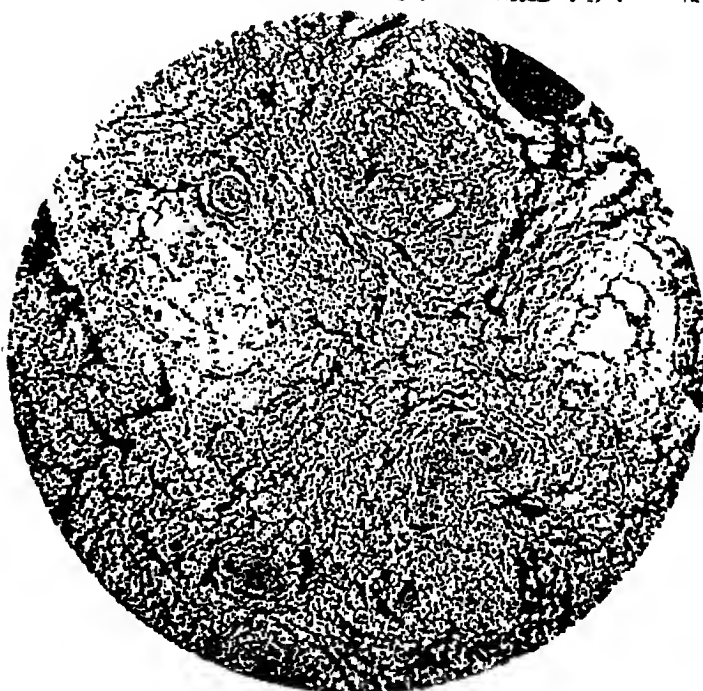
In streptomycin treated cases focal lesions are brought into sharp relief by the relatively empty alveolar spaces surrounding them (figure 2). Such cells as remain are few in number. This paucity of perifocal reaction about fresh or healing foci is best seen about small lesions of the miliary or acinous nodose type, but may also be demonstrated in regions of caseous lobular pneumonia. It is obvious that this effect can best be seen during or immediately after streptomycin therapy, especially in recently developed foci in an individual infected with a sensitive organism, as in Cases 5 and 6 of the present series. Most of the clearing of the shadows observed on serial roentgenograms following the institution of streptomycin therapy is a result of this dissolution of the perifocal reaction. It does, however, leave its mark on healed lesions. The nonspecific capsule usually seen about these lesions is either absent or of small extent. It is believed that this is an important beneficial effect of the drug.

*Effect on tuberculous foci:* The effect of streptomycin on tuberculous foci is difficult to evaluate. Accurate appraisal is possible only in the early cases. In the more advanced cases, healing has already progressed to some degree before the institution of the drug. The problem of determining how much of the healing is a result of streptomycin is therefore difficult.

The evaluation of the effect of streptomycin on the tuberculous foci can only be made by knowing the approximate age of the foci (from roentgenographic studies) and by determining whether the healing changes are greater than those



1a



1b

FIG. 1a. (Upper) Case 1. Miliary tubercle in the lung showing far advanced healing.

FIG. 1b. (Lower) Case 1. Miliary tubercle in the spleen contains a caseous center and a cellular periphery.

of similar age in untreated cases. These changes must be striking and out of proportion to the age of the focus, because healing changes (productive reaction) occur in the natural course of the disease.

*Tuberculous cavities:* General experience thus far has shown that tuberculous cavities do not close with any greater frequency as a result of streptomycin treatment than in untreated cases.

The healing changes in the wall of the cavity, as evidenced by the collagen connective tissue, was greater than would be expected in Case 5, and in Case 6 was far out of proportion to what would be expected in such cases.

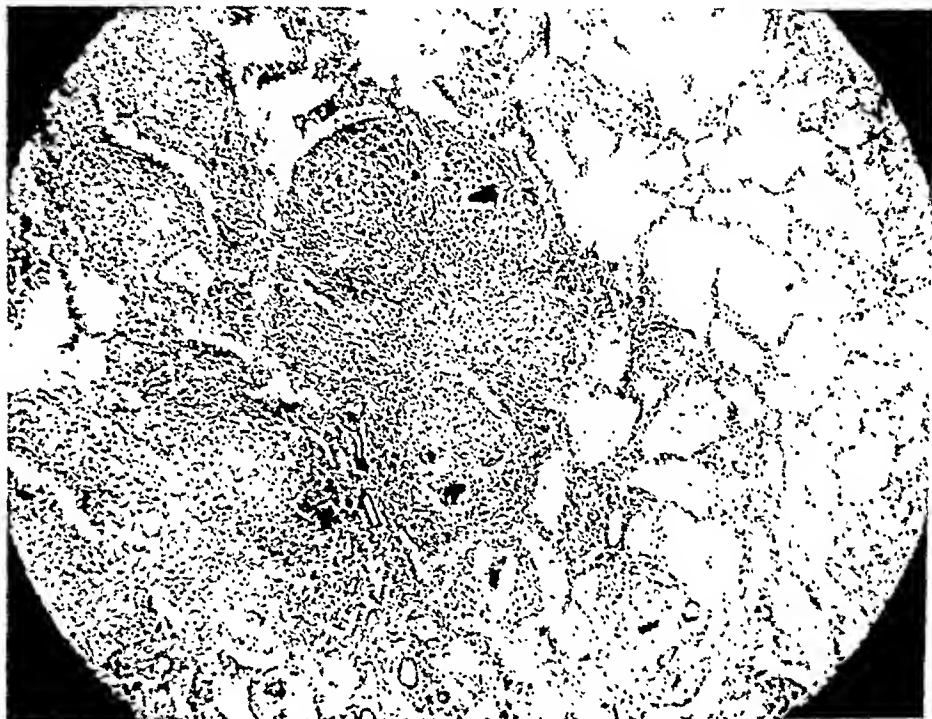


FIG. 2. Case 5. Acirous focus showing a complete absence of perifocal reaction.

*Tuberculous pneumonia:* It is well known that young adult Negroes may develop a rapidly advancing caseous lobular pneumonia, so-called "galloping consumption." The extent and character of the lesions in Case 6 and the duration of the disease fulfill these characteristics, yet there were wide areas of organization of the tuberculous lobular pneumonia. It is believed that this was much out of proportion to the type and duration of the disease where only a minimal productive reaction might have been anticipated.

*Acinous nodose foci:* After miliary foci, these areas show the greatest healing tendency under the influence of streptomycin. This is seen in two ways: (1) there is a greater healing change in the foci; (2) caseous centers are not as frequently seen.

The writers believe that streptomycin does not prevent dissemination of the

disease either through the bronchial or through the lympho-hematogenous routes. The presence of areas of fresh tuberculous lobular pneumonia with caseation in Case 6 after thirty-one days treatment, when large portions of similar lesions show rapid healing changes, speaks for this premise. The presence of fresh acinous nodose foci in Case 5 after twenty-three days' treatment also supports this statement. The fact that miliary type foci were found in the hilar lymph nodes in Cases 4, 5, and 6, and the fact that a very fresh miliary focus was found in the spleen in Case 6 shows that lympho-hematogenous seedings also occur in spite of treatment. It is believed, however, that, although disseminations occur, streptomycin certainly stimulates their rapid healing.

*Miliary tuberculosis:* Much emphasis has been laid on the healing of acute miliary tuberculosis after streptomycin treatment (1, 2, 3). In a previous study one of the writers (4) has shown that healing may occur in acute generalized miliary tuberculosis. Often, however, as the dissemination is secondary to an active extrapulmonary tuberculous process, a new seeding occurs while the first one is undergoing anatomic healing. Thus, it is not unusual to find healed, healing, and active foci, often side by side in the same field.

There are a number of cases in which the writers have observed healing of acute miliary tuberculosis in untreated cases, especially those which occur following the primary complex. In no instance of acute miliary tuberculosis, however, has healing of the miliary foci in the lungs been observed while those in the other organs showed no such changes.

In streptomycin treated cases, quite the contrary is true. The writers' observations, as well as the reports in literature, emphasize the presence of healing and healed foci in the lungs while in other organs some foci may form epithelioid giant cell tubercles, and still others may have caseous centers.

It is believed that this difference between the healing tendency of miliary tubercles in the lungs in comparison to those in solid viscera is consistent with the therapeutic action of streptomycin throughout the body, i.e., its action on the superficial surface. The perifocal reaction (which through its conversion into connective tissue adds to the thickness of the focus) is quickly cleared. The productive reaction soon dominates the process and the tubercle is replaced by connective tissue.

As in solid organs the streptomycin does not exert its influence in the same manner as in the lungs, the healing changes within them will lag behind those in the lung. This may explain why lesions of the same apparent age show different stages of healing in different organs.

*Tuberculous meningitis:* The contrast of the action of streptomycin on the tuberculous process in solid organs and on superficial surfaces is well demonstrated in tuberculous meningitis.

A phenomenal clinical response in tuberculous meningitis has been observed. These cases, in the main, fall into three categories. There is one group in which there is a complete cure after treatment. In the second group a new tuberculous meningitis develops after a temporary cure. Reinstitution of treatment may clear the process if the tubercle bacilli are still sensitive to streptomycin.



This may go on for many months, and the patient finally dies of tuberculous meningitis. In the third group death intervenes shortly after treatment is instituted.

There are two important factors which must be considered in evaluating these results: 1. It is fairly generally accepted that tuberculous meningitis is the result of a rupture of a tuberculous focus into the meninges. These foci are either the result of seeding from the primary complex or from an acute miliary tuberculosis. 2. Boxer (5) has shown that streptomycin does not penetrate brain tissue except in very minute quantities and may be recovered from the cerebrospinal fluid in slightly larger amounts.

In the first group, a complete cure may be explained in the following manner. After one focus had poured its contents on to the free surface of the brain, the bacteriostatic action of streptomycin stimulated a healing of the focus and the resorption of the meningeal exudate. A permanent cure is then possible, if no new tuberculomata form in the brain, or if those tuberculomata already present do not rupture into the meninges. The great difficulty in treating such cases is that the source of the hematogenous dissemination, e.g., skeletal or urogenital tuberculosis, is in a solid organ and therefore not easily affected by streptomycin. Thus, new disseminations will take place and with repeated seedings the opportunity for tuberculomata to develop in the brain is enhanced.

In the second group, there are multiple foci in the brain with multiple ruptures into the meninges. Thus, after resolution of the exudate following the first attack of meningitis, the process is repeated after a second rupture. The patient continues to live through these episodes while the organism is still sensitive to the drug.

In the third group, the lack of success may be the result of an infection caused by a resistant organism or the result of a pouring out into the meninges of an overwhelming exudate by one or many foci.

*Gastro-intestinal tuberculosis:* Gastro-intestinal lesions were seen in only one case in the present series (7). In a series of 885 cases which are now under study, the overall incidence of gastro-intestinal tuberculosis in cases of chronic pulmonary tuberculosis is 72 per cent. Among patients who died between the sixth and twenty-fourth months of their disease, this incidence rises to 88 per cent. Many other authors have reported a similar high incidence. It is especially striking, then, that the only case in the present series with these lesions was one in which a year had elapsed between cessation of treatment and death and in which the infecting organisms were very resistant to streptomycin.

*Laryngo-bronchial tuberculosis:* In a recent study laryngeal tuberculosis was found to be present in 37.5 per cent of 811 cases, 65 per cent of these cases occurring in patients whose chronic pulmonary tuberculosis was less than two years in duration (6). Laryngeal lesions were only found in Cases 2 and 7 in the present series. The lesion in the former was a miliary tubercle which probably occurred between treatment and death. The tuberculous ulcer in Case 7 is not unexpected as a full year intervened between treatment and death.

There is an apparent discrepancy in the presence of an ulcerative tuberculous

lesion in the bronchus in Case 4. Although this lesion was present during treatment, it probably owed its presence to the distorted physiology of the lung in which it occurred. Shrunk, avascular and fibrosed as it was, no drainage of infected secretions could obtain, so that the bronchi were similar to thick-walled cavities.

### CONCLUSIONS

Streptomycin is an aid in the healing of tuberculosis. It has a much greater effect on tuberculous foci in the superficial surfaces than on the foci in solid organs. The perifocal reaction surrounding tuberculous foci is rapidly and extensively resolved, thus diminishing the amount of fibrosis which would ordinarily occur in this zone.

Tuberculous foci in the lung show a greater tendency to heal than in untreated cases. The contrast of the action of the drug on solid organs and superficial surfaces is best seen in acute generalized miliary tuberculosis where the healing changes in solid organs lag behind those in the lungs.

The greatly decreased incidence of laryngeal and intestinal tuberculosis is also attributed to greater healing on superficial surfaces.

The prolongation of the course of tuberculous meningitis, and in some instances its complete cure, is probably further evidence of its action on superficial surfaces.

Streptomycin does not appear to prevent dissemination of the disease either through the bronchial or lympho-hematogenous routes, but, after such disseminations occur, the drug stimulates their more rapid healing.

### SUMARIO

#### *Alteraciones Anatómicas en la Tuberculosis Consecutivamente a la Estreptomycinoterapia*

La estreptomicina es un auxiliar en la curación de la tuberculosis. Su efecto es mucho mayor sobre los focos tuberculosos superficiales que sobre los que radican en órganos macizos. La reacción perifocal se resuelve rápida y extensamente, mermando así la proporción de fibrosis que ocurriría de otro modo en dicha zona.

Los focos tuberculosos del pulmón revelan mayor tendencia a la cicatrización en los casos tratados que en los no tratados. La diversa acción de la droga en los órganos macizos y en la superficie se aprecia mejor en la granulía aguda en la cicatrización en los primeros se retarda más que en los pulmones.

La gran disminución en la incidencia de la tuberculosis laríngea e intestinal también se imputa a la aumentada cicatrización superficial.

La prolongación de la evolución, y en algunos casos, completa curación, de la meningitis tuberculosa aporta nueva prueba probable de la acción de la droga en las superficies.

La estreptomicina no impide al parecer la disseminación de la enfermedad por vía bronquial o linfohematógena, pero ya sobrevenida la disseminación, la droga estimula una cicatrización más rápida.

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# CLINICAL STUDIES ON ALLERGY TO TUBERCULIN FOLLOWING PRIMARY TUBERCULOUS INFECTION

The Clinical Value of Recognizing the State of Secondary Negative Allergy

RICHARD T. ELLISON

## INTRODUCTION

Not so many years ago it was the generally accepted belief that once allergy to tuberculin developed following a primary tuberculous infection such allergy remained demonstrable through the rest of the life of the individual. Recently that teaching has undergone a complete reversal and it is now well known that demonstrable allergy to tuberculin can be lost (1 to 7).

There is no doubt that the tuberculization of the population of the United States as a whole, and especially those living in cities, has decreased greatly in the past decade, the decrease being a change not only in quantity but in quality. The fewer persons with advanced open tuberculosis has resulted in fewer massive primary infections in the general population and less opportunity for the reanimating superinfections that maintain hypersensitiveness and terminate eventually in phthisis (8, 9). Most of the primary infections at the present time are so minimal that they can only be recognized when a positive tuberculin reaction develops.

With the complete healing of these minimal infections, the allergy to tuberculin produced by them is lost and the individual becomes a negative reactor again. If this development of allergy to tuberculin was the only result of such minimal tuberculous infections, its loss would leave the body in its virginal primitive state and there would be no necessity to divide negative reactors into two groups. But allergy to tuberculin is not the only change in the body that results from these short-lived infections and the other changes must also be taken into consideration.

With the primary infection a varying degree of resistance to all subsequent tuberculous infection is acquired and the primary complex leaves anatomical changes that can in many cases be demonstrated by physical examination and by roentgenography. Such an individual differs then, even though he possesses no demonstrable allergy to tuberculin, from one who has not passed through a primary tuberculous infection. This necessitates dividing all individuals who have a negative allergy to tuberculin into two categories, those who are in a state of *primary negative allergy* and those in a state of *secondary negative allergy*. It is with the development, detection, and possible significance of the state of secondary negative allergy that the present paper deals.

The concept that there are different types of negative reactors to tuberculin is not new and what is here termed the state of secondary negative allergy has been described before under a variety of terms. Some that have been used are "positive anergy," "tuberculin desensitization," "infratuberculinic allergy,"

"latent allergy," and "extinction of allergy." Paretzky (10) divided all negative reactors to tuberculin into five separate groups.

#### HYPOTHESIS

It would be well at the very beginning to outline briefly the *working hypothesis* relating to the development of the state of secondary negative allergy on which this presentation is based.

When virulent tubercle bacilli enter the body in sufficient numbers to overcome the first line of defense of the host, they cause a primary complex to develop. The involvement of the hilar and mediastinal lymph nodes as part of this primary complex leads to a fixation of the hilum which presumably results in certain anatomical and physiological changes in the upper part of the lung, especially on the right side, and possibly in the muscles and soft tissues about the shoulder girdle (18). At the same time that these anatomical and physiological changes are taking place, certain other mechanisms are being developed the most easily demonstrable of which is allergy to tuberculin. In the body tuberculin allergy brings about certain changes in the reaction of tissues to subsequent contact with tubercle bacilli. Certain but not all of these changes are well recognized but *as to whether they are an asset or a liability to the organism as a whole is still a matter of debate*. The principal changes that allergy brings about are a greater degree of inflammatory reaction and an earlier formation of tubercle following further contact with tubercle bacilli. The other mechanisms, chiefly of a defensive nature, called into play by primary infection with tubercle bacilli are grouped under the term acquired resistance. These consist of a limitation of the spread of tubercle bacilli from the point of subsequent inoculation, a greater ability to destroy tubercle bacilli *in situ* and a limitation of the proliferation of bacilli. At present there is no qualitative or quantitative clinical test for these mechanisms although their existence is easily demonstrated in animal experiments (1, 11, 12).

If the defense mechanisms are adequate, the primary complex begins to heal and this healing is usually most complete in the primary focus. The lymph node component of the primary complex heals more slowly and less completely. It is in the incompletely healed tracheobronchial and mediastinal nodes that infection may lie dormant for years, maintaining a state of positive allergy in the body and serving as a reservoir from which a devastating spread of tubercle bacilli may occur at any time.

Until recent years it was thought that this incomplete healing was the only possible outcome of a primary tuberculous infection other than the subsequent development of phthisis somewhere in the body. Recently it is being more widely recognized that the primary complex of tuberculosis may heal so completely that the contained bacilli at first become nonviable and eventually die and are destroyed. While this complete healing in a bacteriological sense undoubtedly occurs more frequently in minimal primary infections, it is also becoming apparent that in many cases the primary complex may be sufficiently extensive for calcium to be deposited in the scar and yet eventually become sterile.

With the disappearance from the completely healed primary complex of the specific tuberculo-protein, the stimuli for the continuation of the mechanisms caused by it are lost. Both allergy and acquired resistance begin to diminish in intensity and eventually the former falls below the level of clinical detection. It should be recognized that these two mechanisms are independent of each other and this is especially true of the rate at which they subside after the stimulus to their production is removed. It is impossible to determine exactly how long allergy remains demonstrable after all tubercle bacilli are destroyed, but probably not for longer than a few months (9). The forces of acquired resistance, however, seemingly persist for a matter of years (9) although in a few individuals they also may entirely disappear.

It is also a most important concept of this hypothesis that, if allergy to tuberculin eventually fades out, either all tubercle bacilli in the body have died and their bodies have been destroyed or they have been so completely isolated from the rest of the body that they will eventually die and in the meantime are no longer a source of further infection. As a corollary to this, the reappearance of allergy to tuberculin once it has been lost can only be a result of exogenous reinfection.

From this brief outline of the course of events in the body following infection with tubercle bacilli, it is obvious that the state of secondary negative allergy has some significance and its detection therefore is important. How then can the negative reactors to tuberculin be separated into a primary negative group and a secondary negative group?

#### THE STATE OF SECONDARY NEGATIVE ALLERGY

At present there are conceivably three ways of determining the previous existence of a primary tuberculous infection and thereby establishing the existence of the state of secondary negative allergy. These differ in the positiveness of their proof and also in the readiness with which they will, at present, be generally accepted. The first will prove a previous tuberculous infection no matter where the primary complex is located. The second and third will detect only a primary pulmonary involvement. These three ways are: (1) record of a previous positive reaction to tuberculin; (2) roentgenographic evidence of a previous primary complex in the lungs; and (3) evidence, on physical examination, of hypoventilation of the pulmonary apices with retraction and atrophy about the shoulder girdle (18).

*Frequency of secondary negative allergy:* Before starting a detailed discussion of the clinical value of recognizing the state of secondary negative allergy, it is necessary to consider the frequency of its occurrence. Do those so classified constitute a large enough part of the population to be of significance and, if so, is it the same size in all segments? In certain groups, comprising children from contact families and young women from the general population, studied by the writer by the above mentioned methods, there is a wide spread in the frequency of occurrence of this state (table 1). From the data in this table it would seem that the state of secondary negative allergy comprises a proportion of all negative

reactors that varies widely with age and amount of contact, but that, in certain groups, may closely approach 100 per cent. This is a surprising and significant finding and its recognition is of paramount importance in any study of the epidemiology of tuberculosis.

*Persistence of secondary negative allergy:* Another question that might be asked regarding the state of secondary negative allergy concerns its permanence. During the present studies most of the individuals observed had repeated tuberculin tests. It was found that there were a certain number in whom the reaction fluctuated between positive and negative and that the more frequently these tests were done the more often was this situation encountered. Thus it appears that the state of secondary negative allergy, like the state of positive allergy, is not necessarily permanent, but that in the same individual allergy may fluctuate several times. The fact that allergy can fluctuate in most cases has not been appreciated by many investigators because in their studies when an individual previously negative has developed a positive reaction to tuberculin, such persons have not been retested.

TABLE 1

*Distribution by age groups of persons reacting negatively to tuberculin expressed as percentages of the group totals.*

| Age.....                | CONTACT FAMILIES (WHITE AND NEGRO) |      |       |       | GIRLS ENTERING<br>SCHOOL OF NURSING |
|-------------------------|------------------------------------|------|-------|-------|-------------------------------------|
|                         | 0-4                                | 5-10 | 11-14 | 15-18 |                                     |
| Primary negative.....   | 60                                 | 24.5 | 20    | 4     | 53                                  |
| Secondary negative..... | 40                                 | 75.5 | 80    | 96    | 47                                  |

It has previously been emphasized that allergy to tuberculin is not the only mechanism that is brought into operation following a primary infection. Acquired resistance is also stimulated and is added to whatever degree of native resistance the individual may possess. The two mechanisms, allergy and acquired resistance, are not intimately bound together but can fluctuate independently of each other. Part of the general working hypothesis is the concept that in minimal infections tubercle bacilli may be completely destroyed, thereby removing the stimulus for the continuation of these mechanisms. Of the two, allergy presumably diminishes more rapidly and probably disappears within a matter of months. At the same time acquired resistance is becoming less but the rate of decline is slower and some degree of protection may exist for years (1). In the normal course of events this waning resistance is augmented from time to time by minimal reinfections, but in a few instances reinfection may not occur until acquired resistance has entirely disappeared. If this reasoning is correct, it is obvious that the clinical demonstration of allergy presupposes in most instances a certain degree of acquired resistance. How then can this theory be integrated with the fact that endogenous reactivation and spread occurs in persons with positive allergy. If allergy and acquired resistance can fluctuate independently, it is reasonable to assume that there are times when allergy remains up and resistance is depressed. This can occur when general bodily resist-

ance and specific acquired resistance to tubercle bacilli are depressed by such things as overwork, and by other infections, but especially by an inadequate amount of protein in the diet (5, 6, 7, 8). Rich (9) says: "Particularly does it seem probable that protein deficiency may have an adverse effect upon acquired resistance in infections in general for anti-body is protein and since a dietary deficiency in protein leads to a marked inability to manufacture plasma protein, it is reasonable to suppose that the formation of the anti-body protein of the plasma will likewise be affected." In such a situation endogenous reactivation or lympho-hematogenous spread may occur while allergy is still demonstrable. On the other hand, the fact that a state which should be associated with good resistance is not incompatible with advanced disease is evidenced by the excellent nutrition and general well being of many persons with extensive fibroid phthisis.

*Significance to the individual of secondary negative allergy:* The most important question in regard to the state of secondary negative allergy is whether it is an asset or a liability to the individual.

There is no doubt that the best insurance against developing phthisis is for the person to remain in a state of primary negative allergy as the result of a high level of native resistance. If, however, a primary infection does develop, is it more advantageous to retain a positive allergy or to relapse into a state of *secondary negative allergy*? Persons with a positive allergy to tuberculin harbor a focus of tuberculous infection and therefore constitute the only group subject to the danger of developing phthisis from endogenous reactivation or spread. This focus is sufficient to maintain allergy and, by inference, a relatively high level of acquired resistance. When acquired resistance is depressed in such an individual, it seems probable that the higher the level of accompanying allergy, the more acute the outbreak of pulmonary tuberculosis and the greater the tendency to exudative reactions and caseation. Maintenance of a relatively high level of acquired resistance, as evidenced by the continuation of a positive allergic reaction, is usually adequate protection against exogenous superinfection. Persons with a positive allergy, therefore, need to be protected principally from themselves and this is best accomplished by maintaining a high level of acquired resistance.

Comparing individuals in two states of negative allergy, primary and secondary, it is evident that they can develop phthisis only as a result of exogenous contact with tubercle bacilli. In early childhood the negative reactors to tuberculin are made up of a mixture of individuals with all degrees of native resistance to tuberculous infection. In a tuberculinized environment, with the passage of years those with lesser degrees of native resistance gradually become infected and pass into the group with positive allergy so that by the time early adult life is reached those still in a state of primary negative allergy represent almost exclusively individuals with a relatively high degree of native resistance. That this degree of native resistance is not a true immunity and is not, in contact families, sufficient to prevent eventual infection is evidenced by the entire disappearance of these primary negative reactors in the 14 to 19 year old groups in both white and Negro families (13).

A high degree of native resistance and the ability to develop acquired resistance,



however, leads to rapid control of the tuberculous infection when it does occur. This is shown by the lack of demonstrable evidence of a primary complex, by roentgenographie or other method of examination, when the tuberculin reaction becomes positive. The high level of native resistance plus the resulting acquired resistance holds the infection to a minimal anatomical extent and frequently leads to the early destruction of the invading organisms and the eventual loss of allergy. The individual then again becomes a negative reactor, but this time is in a state of secondary negative allergy with residual acquired resistance.

The older the age group under consideration, the more likely are the primary negative reactors in it to be individuals with a high native resistance and to this extent the less likely are they to develop infection following exogenous exposure, and the less strictly do they need to be protected.

Of the original childhood group composed of individuals with varying degrees of native resistance given the same exposure, those possessing a lesser degree become infected at earlier age levels. In some of these, the infection is sufficient to result in a demonstrable primary complex and to persist throughout the life of the individual, as is evidenced by a lifetime positive reaction to tuberculin. In others, the infection is successfully combated and the tuberculin reaction again becomes negative. The acquired resistance, however, persists in a degree diminishing with the passage of time, but this residual acquired resistance, together with the anamnestic response, is sufficient to greatly modify any subsequent exogenous infection (11). This is evidenced by the failure of a primary complex to develop and the productive character of those reinfections that are demonstrable by roentgenographie examination.

To summarize, it can be said then that the state of positive allergy with its associated acquired resistance is in most cases an adequate defense against exogenous superinfection, but that such individuals are subject to the dangers of endogenous reactivation or spread. Of those who respond negatively to tuberculin, the group of older children and young adults classified as primary negative reactors need protection only from massive or repeated exogenous infection. Their relatively high level of native resistance will either protect them completely from the ordinary contacts or will limit any infection that they may acquire so that only minimal involvement will result. Those persons classified as secondary negative reactors are the most susceptible of all the groups to exogenous exposure to tubercle bacilli and are the group that needs the greatest protection. Their native resistance has been inadequate to protect them from their first infection and even the addition of a certain amount of acquired resistance frequently is not sufficient to protect them from heavy reinfection.

*Possible clinical application of above considerations:* With the above correlation of the clinical data and the theoretical consideration of the question of allergy and acquired resistance following tuberculous infection, it is pertinent to ask what clinical application can be made of the concept of the state of secondary negative allergy to tuberculin. Will such a concept help to explain some of the apparently contradictory facts that have been established and, with it, can the diametrically opposed conclusions of the different men investigating the same subject be

reconciled? The fallacy in many of these investigations is that it has been taken for granted that a negative tuberculin reaction, at no matter what age level it was encountered, was proof that that individual had never been infected with tubercle bacilli. If the concept of the state of secondary negative allergy be accepted, it becomes immediately obvious that all epidemiological studies based on the earlier premise may be appreciably compromised.

For many years the fact that a typical primary complex is rarely seen in adults and yet is the usual response of infancy and early childhood to contact with tubercle bacilli has lead some phthisiologists to the belief that there is a fundamental difference between the two age groups. This belief was strengthened when mass tuberculin surveys showed that many adolescents and adults were negative to tuberculin and yet did not develop a demonstrable primary complex when they later developed pulmonary tuberculosis. This lead to the terms "childhood type" and "adult type" of tuberculosis. The apparent difference in the age groups is readily reconciled by the concept of the state of secondary negative allergy with residual acquired resistance. In such a concept the reaction to the *first* contact with tubercle bacilli is the same at any age. To quote Terplan (14): "It appears, then, from the symposium on primary tuberculous infection of the adolescent and adult, that no sufficiently complete morphological data have become known to prove that the anatomical picture of first infection is different in its extent and effects from the usual primary infection in other age groups." The only real difference in the two age groups is that they differ in the proportion that each contains of individuals with low native resistance who will develop a demonstrable primary complex on contact with tubercle bacilli.

The only real difference in the reaction of groups of children and groups of adults to first contact with tuberculosis is that among children there is a larger proportion with low resistance who for that reason develop a primary complex. Adults who react negatively to tuberculin, and therefore had been considered similar to tuberculin-negative children, are in many instances persons with a high native resistance or those who are in the state of secondary negative allergy with residual acquired resistance.

Another group of clinical investigations in which the results are difficult to explain are those on the incidence of tuberculous infection and disease in medical students, interns, and student nurses. These studies show that when a group of negative reactors to tuberculin turns positive, few if any of them show a typical primary complex. Moreover, of the few who show pulmonary lesions on the chest roentgenograms, the picture is that of a minimal productive infiltration. The discrepancies disappear at once, however, when it is realized that probably at least half of the negative reactors among these young adults are secondary negative reactors with varying degrees of residual acquired resistance and that even the few remaining primary negative reactors represent a thoroughly screened group with relatively high native resistance. With this understanding of the significance of a negative tuberculin reaction in this group, the observed results are exactly what would be anticipated. It would be expected that: (a) there would be few if any cases with a demonstrable pulmonary primary complex;

(b) that in most instances the tuberculin reaction would become positive without any clinical or roentgenographic evidence of disease; and (c) if such evidence were found, the extent of involvement would be minimal and recovery prompt. There is no doubt that many medical students and nurses break down with active tuberculosis, but the greater number of these are individuals who began their medical studies with a positive tuberculin reaction. In them the stress and overwork required to remain in school have worn down their resistance to the point that it has failed to keep their pre-existing infection under control.

*Frequency of primary complex in adult Negroes:* Another clinical observation that has been difficult to explain is the frequency of the occurrence of a typical pulmonary primary complex in the adult Negro. It has long been firmly established that the American Negro is particularly susceptible to tuberculous infection. How then could it so frequently happen that they apparently passed through childhood and adolescence while living in close contact with tuberculosis without becoming infected? The explanation rests on the evidence quoted before (9) that the Negro is less able than the white to maintain acquired resistance. The explanation offered to account for the frequency of a primary complex in the adult Negro is as follows. Practically all of the Negro population becomes infected at an early age but some of them are able to heal this first infection completely and pass into the group of secondary negative reactors with some residual acquired resistance. These individuals are less able than other racial groups, however, to maintain that acquired resistance and it is eventually lost. It takes years to bring this about and they may reach late adolescence or early adult life before they revert to a condition similar to their original childhood state in which there is neither allergy nor acquired resistance. If, when they have reached this state, they again come in contact with tubercle bacilli, they develop a true secondary primary complex. That this is so is evidenced by the frequency with which the remains of a previous infection are found when a fresh primary complex is demonstrated in an adult Negro. Rich (9, page 139) says: "Certainly, in the present writer's experience, the presence of the childhood type of progressive tuberculosis in adult Negroes has by no means excluded the finding of associated older arrested caseous and calcified primary lesions; and Pinner and Kasper (17) in their excellent study of this point report the same observation."

Another situation that is leading to much confusion and mutual misunderstanding among clinical investigators is the finding of pulmonary and tracheobronchial calcifications in persons who have a negative reaction to tuberculin. It has long been known that such calcifications frequently result from a primary tuberculous complex and, as tuberculosis is by far the most frequent chronic pulmonary infection in children, it was assumed that most such calcifications were of tuberculous origin, although admittedly some might be due to other causes. A difference of opinion among clinicians developed, however, when such calcifications were found in children with a negative tuberculin reaction. Those who were firmly grounded in the belief that "once infected with tuberculosis always infected" and that therefore once allergy developed it remained positive for the rest of that individual's life, felt that calcifications in the presence

of a negative tuberculin reaction could not be a result of tuberculosis. Therefore, they have been searching for some extremely common pulmonary disease, severe enough to produce pulmonary calcifications, which disease had existed for generations but so far had eluded clinical detection. Although such diseases undoubtedly exist, the coexistence of calcifications as a result of a tuberculous primary complex and a negative tuberculin reaction can be reconciled by the concept of the state of secondary negative allergy.

*Relation of secondary negative allergy to studies of BCG:* Another field of investigation in which there is a wide difference in the conclusions drawn from clinical study concerns the value of BCG in the control of tuberculosis. There has been both enthusiasm and condemnation for the use of the vaccine but the studies on which both opinions are based have been criticized for lack of adequate control and follow-up. Recently in this country there have been two separate investigations that are seemingly free of these objections. They are comparable in that both comprise studies on large groups of individuals who were given several different batches of BCG vaccine by the same route; in each, an entirely similar group served as controls; and in each, there was adequate follow up for a period of six years of both the vaccinated and control groups. In spite of these similarities, the conclusions reached as to the value of BCG vaccination in the prevention of tuberculosis flatly contradict each other. It is possible that the concept of the state of secondary negative allergy with residual acquired resistance could explain this contradiction.

The investigations in question were conducted in New York City (9) and on various reservations for American Indians (17) and will be referred to as the "New York" and the "Indian" group, respectively.

There is only one thing in which these two studies differ and that is the composition of each group. If the concept of the state of secondary negative allergy to tuberculin is applied to each group, the conflicting conclusions can be reconciled and each be made to fit into a general pattern.

When the reports are examined it will be found, first, that the New York study is composed almost exclusively of infants who received their vaccination before they were one year old. This group, which of course was negative to tuberculin, was presumably composed entirely of primary negative reactors, for it is unlikely that an infant could acquire and completely heal a tuberculous infection in the first year of life. This group of primary negative reactors was composed of individuals with all degrees of native resistance, some high and some low. Comparing the vaccinated group with the control group, the investigators found that there was no difference in the incidence of tuberculosis developing in a five year period after vaccination and they conclude that BCG vaccination is valueless in the prevention of tuberculosis. They say (16): "The figures for the groups were essentially similar, the tuberculosis mortality of the vaccinated cases being 1.41 per cent as against 1.51 per cent for the controls." They also state: "As a public health measure, therefore, the routine vaccination with BCG of children from tuberculous homes is less advantageous than removal of the tuberculous subject from the home."

The Indian study, on the other hand, is composed of a group of "Indian persons

ranging in age from one to 20 years inclusive" (17). From their figures it will be seen that 67.5 per cent of the BCG group and 66.9 per cent of the control group were from age 5 to 14 years inclusive. A possible fallacy in the conclusions drawn by these authors lies in the fact that, because the tuberculin reaction was negative, they considered these individuals to be free of previous tuberculous infection and therefore in a state of primary negative allergy. From what has been said above, this appears improbable. From table 1, which is derived from studies reported elsewhere (13), it can be seen that, in these age groups from contact families, between 75 and 80 per cent of those with no allergy to tuberculosis were classed, according to criteria discussed before, as secondary negative reactors and only 20 to 25 per cent were found to be free of previous tuberculous infection. While it has already been stressed that no two groups were exactly similar, it is of interest to compare contact families in Philadelphia's poorer section with contact families on an Indian reservation. If the same distribution of secondary negative reactors obtained in both groups, instead of being entirely free of tuberculosis, approximately three quarters of the Indians vaccinated were in all probability secondary negative reactors and therefore had varying degrees of residual acquired resistance. This would make the Indian group of negative reactors a highly selected one and this selectivity would be further increased by the consideration that many of these individuals who have survived into the age period in question in a state of primary negative allergy presumably have done so because of a high degree of native resistance. In summarizing their findings in this possibly highly selective segment of their population these authors find: "The comparison for total incidence, (of tuberculosis) cases of all types and deaths, is that of 185 among controls and 40 in the vaccinated. In terms of cases per 1,000 person-years, the rates were 24.3 and 4.7 respectively." This is a significant difference and indicates that the BCG vaccine had afforded a considerable amount of protection against tuberculosis to those who received it.

It is obvious from the above consideration that the segments of the population forming the basis of these two studies are not comparable, due to the differences in average age, length of exposure to tuberculosis, native resistance, and especially the possible unintentional selection of individuals with increased acquired resistance to tuberculosis in the Indian group. If the groups are not comparable, then the results of the studies are not comparable, and both conclusions may be right for their respective groups. How then can these results be interpreted? It would seem that in an unselected group of infants BCG vaccination was unable to so augment native resistance or stimulate acquired resistance as to afford any significant protection against subsequent tuberculous disease. On the other hand, in a group presumably composed principally of individuals with varying degrees of resistance acquired from a previous infection, similar vaccination produced a very satisfactory degree of protection. It would seem that most of those individuals in the Indian group that were vaccinated received a "booster shot" at a time when their acquired resistance was declining and that this situation plus the anamnestic response was what afforded the protection.

From this it would seem that the probable ultimate usefulness of BCG vaccination will be to restimulate a declining resistance in persons who have already healed a previous primary tuberculous infection and are in a state of secondary negative allergy with declining residual acquired resistance.

#### SUMMARY

A working hypothesis is developed to account for the appearance and, in some cases, the subsequent loss of allergy to tuberculin. The concept that acquired resistance persists after this loss of allergy is fundamental to the hypothesis. This state of sensitivity to tuberculin is termed secondary negative allergy with residual acquired resistance.

It is believed that the state of secondary negative allergy occurs with sufficient frequency to make its detection important, although the actual incidence varies in different groups according to their age, economic level, and degree of exposure to tuberculosis.

Secondary negative allergy is not necessarily a permanent state but can be changed into positive allergy by reinfection.

It is pointed out that allergy and acquired resistance are both initiated by the primary infection. When a minimal primary lesion heals completely, however, allergy disappears rapidly, whereas residual acquired resistance persists. In this respect, secondary negative allergy differs from primary negative allergy.

The value to the individual of the different states of allergy to tuberculin is discussed. It is pointed out that positive allergy indicates a bodily state in which exogenous superinfection is difficult to establish, but in which endogenous reactivation or spread is a constant hazard. Primary negative allergy, if maintained because of high native resistance and not because of lack of contact, is undoubtedly the most desirable state. Secondary negative allergy is the state that needs the greatest protection from exogenous reinfection.

The concept of secondary negative allergy with residual acquired resistance has been used to explain and integrate certain clinical observations. It can explain the difference in the resultant pathological pictures when tuberculin-negative children develop for the first time, and tuberculin-negative adults develop for the second time, a hypersensitivity to tuberculin. It can explain the "atypical" clinical picture in most tuberculin-negative medical personnel when they subsequently develop hypersensitivity. It can be used to reconcile the coexistence of pulmonary calcification of tuberculous origin and a negative tuberculin reaction.

Finally the concept of secondary negative allergy with residual acquired resistance can explain and integrate the conflicting opinions as to the value of protective vaccination with BCG. It is suggested that the vaccine is not capable by itself of sufficiently stimulating acquired resistance to afford adequate protection against subsequent exposure, but that it can restimulate and augment a failing naturally acquired resistance.

## SUMARIO

*Estudios Clínicos de la Alergia a la Tuberculina, Consecutiva a la Infección Tuberculosa Primaria*

La hipótesis aquí elaborada permite explicar la aparición y, en algunos casos, pérdida subsiguiente de la alergia a la tuberculina. El concepto de que la resistencia adquirida persiste después de dicha pérdida de alergia es fundamental para la hipótesis. Ese estado de sensibilidad a la tuberculina es denominado alergia negativa secundaria con resistencia adquirida residual.

Opina el A. que el estado de alergia negativa secundaria es suficientemente frecuente para que su descubrimiento revista importancia, aunque su incidencia real varía en diversos grupos conforme a edad, situación económica, y exposición a la tuberculosis.

La alergia negativa secundaria no es forzosamente un estado permanente, pues la reinfección puede virarla a positiva.

Señálase que la alergia e igualmente la resistencia adquirida son iniciadas por la infección primaria. Sin embargo, cuando una lesión primaria mínima cicatriza completamente, la alergia desaparece con rapidez, en tanto que persiste la resistencia adquirida residual. En este sentido, la alergia negativa secundaria discrepa de la primaria.

Discútese lo que representan para el individuo los diversos estados de alergia, indicándose que la alergia positiva denota un estado físico en el cual es difícil establecer una superinfección exógena, pero en el que la reactivación o difusión endógena constituye un riesgo constante. La alergia negativa primaria, si la mantiene una resistencia natural alta y no la falta de contacto, representa sin duda el estado más conveniente. La negativa secundaria es el estado que necesita la mayor protección contra la reinfección exógena;

Utilízase el concepto de la alergia negativa secundaria con resistencia adquirida residual para explicar e integrar ciertas observaciones clínicas. El mismo puede explicar los diversos cuadros patológicos observados cuando niños tuberculino-negativos manifiestan por primera vez, y adultos tuberculinonegativos por segunda vez, hipersensibilidad a la tuberculina. Puede también explicar al "atípico" cuadro clínico notado en el personal médico tuberculinonegativo al manifestar después hipersensibilidad. Puede usarse además para reconciliar la coexistencia de calcificación pulmonar tuberculógena y reacción negativa a la tuberculina.

Por fin, el concepto de alergia negativa secundaria con resistencia adquirida residual puede explicar e integrar las opiniones contradictorias en cuanto al valor de la vacunación protectora con BCG, sugiriéndose que la vacuna no es capaz, de por sí, de estimular la resistencia adquirida lo suficiente para facilitar protección adecuada contra la exposición subsiguiente, pero puede sí excitar de nuevo y acrecentar una resistencia adquirida naturalmente y en vías de extinción.

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## EDITORIAL

### Present Status of Therapeutic Pneumothorax

From having been in the twenties a principal weapon in the treatment of pulmonary tuberculosis, artificial pneumothorax today is in danger of being too neglected. The early enthusiasm for this therapy has felt the chilling effects of statistics on the frequency of empyema, inexpandible lung, and relapse after re-expansion of an effectively collapsed lung.

The list of indications for therapeutic pneumothorax has undergone such repeated withdrawals that, for some physicians, not many remain. For the zealot of pneumothorax, it is discouraging that the types remaining, which are considered to be suitable for the treatment, are the very ones in which the possibilities of permanent complete success have been definitely reduced.

Pleurisy is a more frequent complication when the parenchymal disease is exudative and producing toxic symptoms. Time should be allowed for the inflammation to subside somewhat before beginning collapse therapy. Sometimes it is then possible to avoid it entirely. Or, if pneumothorax is considered to be necessary after two to six months of bed-rest, pleural complications are likely to be less frequent.

Phrenic nerve interruption permits the avoidance of collapse treatment in some cases. It has the advantage of being accompanied by practically no complications. When the disease is relatively fresh, exudative, usually subapical or in the lower or middle thirds of the lung field, and if the cavity is less than 2 cm. in diameter, success with the phrenic nerve operation is frequent. It certainly avoids the use of pneumothorax in a fair number of such cases. Another type of disease which in the past was often treated with pneumothorax is a lesion which is predominantly basal, usually with a large cavity and not too much surrounding infiltration. Some such lesions will close after phrenic paralysis, if not alone then in combination with pneumoperitoneum.

The developing popularity of thoracoplasty has taken many cases away from pneumothorax and properly so. The writer formerly would use pneumothorax virtually solely on the basis of the condition observed at the time (*e.g.*, sputum containing tubercle bacilli and a cavity which was enlarging or remaining stationary) without too much attention to the fact that the extent and type of disease were such that relapse after re-expansion was probable. Cases of this sort include the predominantly fibrous lesions principally confined to the upper third of the lung. The procedure was to try pneumothorax first and, if it failed, to perform a thoracoplasty. When the pneumothorax succeeded, too many of these cavities reopened in the several years after the lung had been allowed to re-expand. The present practice is to do a primary thoracoplasty in such cases.

The development of knowledge of the relationship of bronchial tuberculosis to relapses and unexpected setbacks of the parenchymal lesion has had a definite effect on pneumothorax therapy. Today, it is unlikely that atelectasis will be

mistaken for tuberculous pneumonia. It is now appreciated that failure of the lung to re-expand after pneumothorax is not always due to rigid fibrosis of the lung. Bronchoscopy is practically a *sine qua non* before attempting pneumothorax therapy and this form of collapse is contraindicated in the presence of a stenosing lesion of a main or secondary bronchus. If pneumothorax is induced when the bronchial lesion is merely a localized congestion of an upper lobe branch, the bronchial lesion may extend to the lower lobe branch despite the pneumothorax. As a consequence, atelectasis of the subsidiary lobe may take that much more respiratory space from the patient. In addition, bronchial disease has been blamed for many of the pleural complications of pneumothorax. The writer questions this and believes rather that most pleural complications are due to beginning the collapse while the disease is too inflamed. Another source of difficulty is, of course, the continuation of pneumothorax in the presence of adhesions which interfere with a good mechanical collapse.

It should hardly be necessary today to point out that pneumothorax should be considered a tentative procedure. If the lesional area can be effectively collapsed away from the chest wall and preferably also from the upper mediastinum, then only should it be maintained, unless, of course, no other measure can be substituted. Frequently it is necessary to perform a pneumonolysis within the first month of collapse therapy to obtain such a collapse. A permanently successful effect is seldom obtained when the cavitory portion is pressed against and directly attached to the chest wall. Cavities which close very slowly, requiring over three or four months, frequently reopen after re-expansion. When thoracoplasty or other surgical means cannot be performed, such a mechanically poor but clinically effective collapse may be maintained. *Except in such a circumstance, however, the tentative procedure of pneumothorax should be abandoned as early as possible, practically always within a month or two at the latest.*

The writer formerly achieved an occasional successful result with pneumothorax in the periodically sick patients whose symptoms were due to infection behind stenotic bronchi and bronchiectasis. Now such patients would be subjected to resection of a lobe or lung.

In the past, pneumoperitoneum was used by many only for the hopeless bilateral cavernous case. For some physicians that is becoming the position of pneumothorax today. Certainly pneumoperitoneum, combined with a phrenic nerve interruption on the worse side, will sometimes tide sick patients over the stage of most active inflammation so that subsequent collapse measures have a much better chance for success. It must be recognized that the enthusiasts for pneumoperitoneum, influenced by the fact that its complications are less than those of pneumothorax, are encroaching more and more on the use of pneumothorax in the more favorable cases. Thus pneumoperitoneum is being used in the types of case in which pneumothorax is most indicated, *i.e.*, patients with unilateral disease which is not too extensive and is usually exudative.

There are certain features about cavities which influence the choice of treatment. The large thin-walled cavity, usually designated a "tension cavity," responds better to a short term Monaldi operation followed by thoracoplasty than

to pneumothorax. Because some basal cavities collapse after phrenic nerve interruption, that procedure should precede the use of pneumothorax in such cases. Cavities situated near the surface of the lung are notoriously dangerous under pneumothorax treatment.

What then is the position of pneumothorax today? Naturally it is advisable to try to avoid the procedure whenever possible. A patient in a febrile stage, with exudative disease and a cavity, should receive a period of bed-rest. If improvement follows and yet some artificial help seems to be indicated, methods less dangerous than pneumothorax should be tried initially, such as phrenic interruption or pneumoperitoneum. The presence of bronchial disease, at least the stenotic and ulcerogranulation tissue type, should be excluded before trying pneumothorax. Moreover, pneumothorax should not be employed if the age or the extent and the type of lesion argue against permitting re-expansion. The writer long ago abandoned the practice of using pneumothorax as a preliminary to attempting thoracoplasty. Pneumothorax should be regarded as a tentative procedure which must prove its value within a few months.

Such a program necessarily greatly limits the use of pneumothorax therapy. Nevertheless, by following this plan tuberculous empyema and serious serous pleurisy are rarely encountered.

Because streptomycin therapy is so new it has not been added to the list of factors which may limit the use of pneumothorax. It is reasonable to believe, however, that chemotherapy is going to enable us to avoid pneumothorax in some patients and will make pneumothorax a safer procedure in others by neutralizing toxic symptoms.

To sum up: Pneumothorax is not employed as much today as formerly although it is a much safer procedure than earlier studies would indicate. The latter fact is probably a result of better choice of patients in the ideal group, a period of prior bed-rest sufficiently prolonged to permit a subsidence of the most active inflammation, early pneumonolysis, and early cessation of pneumothorax if effective collapse does not seem possible. Pneumothorax is contraindicated if other measures are available in stenosing and ulcerogranulomatous bronchial tuberculosis. When thoracoplasty is possible and the extent and age of the disease favor the possibility of exacerbation after re-expansion, a primary thoracoplasty is advisable without a prior attempt at pneumothorax.

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# THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

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**Tuberculosis of the Tongue.**—A patient with advanced pulmonary tuberculosis developed a proved tuberculous ulcer of his tongue subsequent to a trauma. Following treatment with streptomycin the ulcer healed completely while the pulmonary condition did not improve.—*Treatment of Tuberculous Ulcer of the Tongue with Streptomycin*, H. Wolfer, I. Hirshleifer & R. Shapiro, J. A. M. A., January 24, 1948, 136: 249.—(H. Abeles)

**Tuberculous Cervical Adenitis.**—The treatment of tuberculous cervical adenitis has gone through a number of phases. Extensive surgical extirpation fell into disrepute and was replaced by nonsurgical measures such as heliotherapy and roentgen therapy. The former treatment is lengthy and unavailable to most patients. The latter, while efficacious, leaves unsightly scars. Aspiration of abscesses resulting from extension of the tuberculous process is to be condemned. Incision followed by curettage also is disapproved; the results are very poor and occasionally disseminated tuberculosis results. The author proposes a revival of surgical treatment. Good anesthesia is desirable in order to avoid overdilatation of the neck veins. The surgeon should be trained in dissection of the neck. Diseased tonsils and adenoids should be removed. Complete local dissection of the involved group of nodes should be carried out. Where abscess formation has resulted, and the skin is involved, the unhealthy portion is excised and the wound is packed with vaseline gauze. Provision should be made for a convalescence of two to three months.—*Tuberculous Cervical*

*Adenitis*, H. Bailey, *Lancet*, February 28, 1948, 1: 313.—(A. G. Cohen)

**Tuberculosis of the Pancreas.**—In Argentina, 7 cases of this very rare localization of tuberculosis have been published. Another case is added by the authors. An 18-year-old girl was treated over a period of one year for intestinal tuberculosis. The autopsy showed hematogenous tuberculosis of most of the intestinal organs. The pancreas was surrounded by a voluminous conglomeration of caseous glands. The organ itself was studded with numerous seed-like nodules, especially in the head. Histologically, there was massive central necrosis of the lobules with thrombosis of the central arteriole. In the periphery of the lobule the necrosis was less intense. Numerous lymphocytes and some fibroblasts and histiocytes were found in this area. The necrosis was contained by the interlobular wall. Occasional acid-fast bacilli were found.—*Tuberculosis hematogena del pancreas*, F. Gonzalez, R. I. Latienda & E. Erbelli, *Arch. argent. de fisiol.*, 1946, 22: 37.—(W. Swienty)

**Genital Tuberculosis.**—Latent genital tuberculosis in females is more common than heretofore suspected. Endometrial biopsies are of value only if the tuberculous process reaches the endometrium. The author performed cultures for tubercle bacilli on 140 specimens of menstrual fluid from 80 women including 10 with known endometrial tuberculosis and 2 suspects. Nine positive cultures were obtained from 6 different women, in-

cluding 2 who had positive biopsies. Cultures in 19 others revealed nonpathogenic acid-fast bacilli.—*Detection of Latent Genital Tuberculosis by Culture of Menstrual Discharge*, I. Halbrecht, *Lancet*, December 27, 1947, 2: 947.—(A. G. Cohen)

**Tuberculous Lupus Treated with Vitamin D<sub>2</sub>.**—The author reports marked improvement in the clinical condition of a 36-year-old patient suffering from tuberculous lupus and from arthritis, following treatment with vitamin D<sub>2</sub> for a period of about twelve weeks. The dosage was 240,000 units (6 mg.) of an alcoholic solution given daily by the oral route during the first month, and 120,000 units (3 mg.) daily during the following months. The treatment given varied somewhat from that recommended by Charpy (600,000 units three times for one week, twice a week for one week and once a week for three weeks). In spite of the larger doses given, no signs of intolerance were manifest. During the first weeks, blood calcium and urinary calcium increased. In the later months there was spontaneous reduction of calcium excretion. Tuberculous arthritis in the right knee showed definite improvement during the treatment. The patient had had lupus of the right cheek for twenty years. Biopsy of tissue at the periphery of the lesion showed Langhans' giant cells and epithelioid cells surrounded by a lymphocytic infiltrate. The right knee, which was the seat of subacute inflammation and hydrarthrosis, was swollen and tender. Culture of aspirated cloudy fluid, 35 cc. in amount, resulted in the growth of tubercle bacilli. A patch tuberculin test at the beginning of treatment gave a four-plus reaction, at its close only a two-plus reaction. A second aspiration of the knee at about the same time yielded barely 7 cc. of blood-stained fluid. Cultures and animal inoculation of portions of this were negative after four weeks. In conclusion, the author believes the administration of unusually large doses of vitamin D<sub>2</sub> was of great benefit to his patient. However, he warns physicians that patients receiving such doses should be

under the strictest medical supervision. Clinical signs of toxic effect, or of important modifications of blood calcium or urea would be indications for temporary or complete abandonment of the treatment.—*Considérations sur le traitement du lupus tuberculeux par la vitamine D<sub>2</sub>*, J. Grandbois, *Laval med. (Quebec)*, September, 1947, 12: 829.—(A. T. Laird)

**Treatment of Tuberculous Cystitis.**—In 4 patients who had undergone nephrectomy for renal tuberculosis, there was a persistent cystitis. Treatment consisted of transplanting the remaining ureter into the pelvic colon. Good symptomatic results were obtained in all cases.—*Tuberculous Cystitis: Transplantation of Remaining Ureter*, F. C. Pybus & D. T. Jones, *Lancet*, February 21, 1948, 1: 280.—(A. G. Cohen)

**Tuberculous Cystitis.**—Three cases are reported. The first was characterized by "the golf hole ureter"—the gaping hole in the bladder wall produced by tuberculous involvement of the ureter. Nephrectomy established the diagnosis of tuberculous pyonephrosis and ureteritis. The second case had bilateral gaping ureteral orifices, produced not by ureteral traction but by "increased intravesical pressure and incompetence of the valve mechanism." The third case, at cystoscopy, revealed mucosal ulceration around a golf hole ureteral orifice. Intravenous pyelogram indicated a filling defect in the bladder, around the right ureteral orifice. Although a filling defect is usually caused by neoplasm, the diagnosis here was ulcerating tuberculosis pyelonephritis, ureteritis and cystitis.—*Tuberculous Cystitis: Notes on Three Cases*, A. S. Johnston, *Brit. J. Radiol.*, February, 1947, 20: 61.—(L. Hyde)

**Tomography of the Spine.**—Tuberculosis of the spine is first noticeable in the X-ray film as a diminution of the space between the vertebral bodies, with decalcification of the adjacent portions of bone. As caries pro-

gresses some collapse occurs, and several vertebral bodies may be involved. Ordinary anteroposterior and lateral X-rays are useful in determining the extent and progress of the disease. Tomography is of special value, however, in overcoming difficulty in such areas as the first and second cervical vertebrae, the cervical-dorsal region, and the lumbosacral area, where overlapping structures may interfere in delineation of bony disease. In the region of the first and second cervical vertebrae, a good view of the diseased area may be obtained from an ordinary lateral film, but in the anteroposterior X-ray film the area is usually obscured by the lower jaw. In the cervical dorsal region, tuberculous disease may be delineated with plain films, but tomography may be very helpful in more accurate definition. Tuberculous disease of the sacrum is rare except in conjunction with disease of the sacroiliac joints. Tomograms may be of value in special cases. A brief description of the radiographic technique is given.—*Tomography of the Spine in Tuberculous Disease*, S. G. Wood & M. C. Wilkinson, *Brit. J. Radiol.*, October, 1947, 20: 418.—(L. Hyde)

**Addison's Disease.**—The author describes and analyzes the incidence, with age and sex distribution, and the findings in 38 cases of Addison's disease—17 males and 21 females—diagnosed from 1921 to 1945 in several hospitals in Helsinki, Finland. In 14 cases a tuberculous etiology could be established; 8 of those were confirmed by autopsy, revealing adrenal tuberculosis, while 6 had a history or signs of tuberculosis in organs other than the adrenals. In two cases the X-ray finding of calcified lesions in the adrenal area indicated the tuberculous etiology. Other causes of the syndrome were atrophy, sclerosis or injury of the adrenal gland, metastatic carcinoma and endocarditis lenta. More than 50 per cent died within two years from the onset of the symptoms; the longest duration was ten years. The most recent cases were treated with a low potassium diet, sodium chloride, vitamin C and Cortiron injections.—*Clinical*

*Findings in Addison's Disease*, O. Helve, *Act. Med. Scand.*, June, 1947, 128: 289.—(O. Pinner)

**Congenital Tuberculosis.**—In a previous communication, the authors reported the case of a 17-day-old infant who died of tuberculosis which was thought to have resulted from aspiration of infected amniotic fluid. The mother showed no signs of clinical tuberculosis, but the Mantoux was positive. Nine months later, she developed tuberculosis of one eye and then progressive pulmonary tuberculosis from which she eventually died. There was no autopsy. Thus, in her case, placental involvement was the first clinical manifestation of hematogenous tuberculosis.—*Aspiration Type of Congenital Tuberculosis: Further Communication*, W. Pagel & S. Hall, *Tubercle*, February, 1948, 29: 32.—(A. G. Cohen)

**Erythema Nodosum and Tuberculosis.**—The relationship between erythema nodosum and tuberculosis is an unsettled question. Geographical factors are important. Erythema nodosum sometimes is found in lymphogranuloma venereum, sarcoidosis, pneumonia, syphilis and staphylococcus infections. It is evident that under European conditions the principal causes are tuberculosis and hemolytic streptococcus infections. The relative importance of the two factors varies from one country to another. Recent work in Sweden on 178 cases of erythema nodosum in adults showed only 58.4 per cent to be tuberculous, while at least 16.9 per cent were due to hemolytic streptococcus and the remainder to unknown factors. The author analyzes his own material in Norway from 1937 to 1947. In these cases, 50.5 per cent occurred between the ages of 16 and 30. He wonders if there is not a predisposition in this particular age group. The tendency to appear in certain families is noted. All patients were examined by the Pirquet test; if this was negative, a Mantoux was done. By this means, 86.5 per cent were found positive to the Pirquet, with an additional 2.5 per cent positive to Mantoux. A conversion of tuberculin test

from negative to positive was found in 29 per cent. Tubercle bacilli were found in gastric contents in 57 cases; with an additional case of primary tuberculosis of the urogenital tract, there was a total of 58 cases or 29 per cent with proved primary tuberculous infection. In addition, primary tuberculosis is highly probable (1) when tuberculin conversion (less than two years between last negative and first positive) is found, together with a roentgenogram characteristic of primary tuberculosis, (2) when a vesicular Pirquet reaction is combined with a characteristic roentgenogram, and (3) when a vesicular Pirquet reaction is found in children under 5 years of age. These criteria were fulfilled in 52 cases (26 per cent). Thus, there were 55 per cent in which tuberculosis was certain or highly probable. Primary tuberculous infection also is probable in cases showing conversion of tuberculin reaction but with a negative roentgenogram. This was found in 18 cases (9 per cent), making a total of 64 per cent in which tuberculosis may be considered certain or probable. In 12 cases (6 per cent), there was weighty clinical and/or bacteriological or serological evidence of streptococcus infection. In 4 of these, sulpha drugs seem to have been the cause. On 7 occasions, erythema, nodosum appeared during pneumonia, on 5 occasions during rheumatic fever and 6 times during nontuberculous hilar adenitis. Thus, there was positive evidence of nontuberculous etiology in 15 per cent. Of the remaining 38 cases, tuberculosis could be definitely excluded in 22. Thus, in 52 cases (26 per cent) there was overwhelming evidence of a nontuberculous etiology. The author concludes that not more than two-thirds of cases of erythema nodosum are due to tuberculosis. Still, every tuberculin-positive case with erythema nodosum must be treated for tuberculosis unless a thorough examination can rule this out. The best guide to an etiological diagnosis seems to be a vesicular Pirquet reaction. Affections of the eye were found in 5.5 per cent. The importance of episcleritis in the diagnosis of tuberculosis is stressed. Of 44 electrocardiograms, 41 were normal.—*Further Investigations Concerning the*

*Relation between Erythema Nodosum and Tuberculosis, H. J. Ustvedt, Tubercle, December, 1947, 28: 247.—(A. G. Cohen)*

**Examination of Sputum for Tubercle Bacilli.**—Gastric lavage is an inconvenient method for obtaining material for bacteriologic examination. In 1941, the laryngeal swab method was introduced. The report is a comparative study of the two methods. The patients were all known tuberculous cases who had become sputum free or had scanty sputum which was negative by smear and culture. In 58 patients, a laryngeal swab was made on three successive days, while gastric lavage was done on the second day. In 115 patients, only one of each was done, while 20 patients had one gastric lavage and two swabs. All the material was cultured by methods which are described in detail. No direct smears were made. Better results were obtained with the gastric lavage than with only one swab; where there were three swabs, the results were better than with gastric lavage. However, if three tubes were inoculated with the same gastric washings, better results were obtained than from three laryngeal swabs. The swab is preferable because it is less unpleasant for the patient, creates less work for the nurse and is easier for the laboratory to handle.—*Examination for Tubercle Bacilli by Gastric Lavage and by Laryngeal Swab: A Comparative Study, H. G. Hounslow & G. Usher, Tubercle, February, 1948, 29: 27.—(A. G. Cohen)*

**Dubos' Medium for culture of *M. tuberculosis*.**—The use of a mild reagent (2.5 per cent solution of ammonium carbonate) for homogenization and concentration of tuberculous sputa and the addition of penicillin (0.05 to 2 units per ml.) to the culture medium permitted the successful application of Dubos' medium to the routine culture of *M. tuberculosis* from sputum. Of 400 examined sputa, 34 (8.5 per cent) were positive by culture method and negative by microscopic examination. The use of Dubos' medium offers the advantage of a rapid (within eight to fifteen days) culture diagnosis of sputa containing relatively small





$1:6.4 \times 10^5$ . Activity *in vitro* decreases with increasing size of the inoculum and with increasing acidity of the medium; it is little affected by the presence of serum. Licheniformin is moderately toxic for mice, high dosages causing death and repeated smaller doses causing damage to the kidneys.—*Licheniformin, an Antibiotic Substance from Bacillus Licheniformis, Active against Mycobacterium Tuberculosis*, R. K. Callow, R. E. Glover, P. Darcy Hart & G. M. Mills, *Brit. J. Exper. Path.*, December, 1947, 28: 418.—(H. J. Henderson)

**Antibiotic Activity of Actinomycetes.**—This paper reports three agar plate methods (the cross-streak, the cylinder plate and the streak plate) and the various media which have been used to select actinomycetes with antibiotic properties, and to test filtrates and concentrates derived from these. The streak plate method with virulent human tubercle bacillus (H37Rv) is useful as a relatively rapid procedure for screening cultures in the search for new antibiotics. If a streptomycin-resistant strain of H37Rv is also streaked on the plate, antibiotics bearing a relationship to Streptomyces griseus may be detected. A smooth opaque layer of growth may be obtained by seeding pour plates with H37Rv. Filtrates and concentrates in cups will give inhibition zones, though quantitative measurements are difficult to make because the zones are not always sharply defined. Pour plates, seeded with tubercle bacilli and streaked with actinomycetes, are useful in the search for cultures with tuberculostatic properties. The plates may be seeded with H37Rv or with H37RvR (resistant to streptomycin) and cross-streaked with various strains of actinomycetes. The avirulent, rapidly growing strain 607 is not suitable for this purpose, since some strains of actinomycetes which inhibit the virulent H37Rv strain do not inhibit, under the same conditions, strain 607.—*Plate Methods for Testing Antibiotic Activity of Actinomycetes against Virulent Human Type Tubercle Bacilli*, E. H. Williston, P. Zia-Walrath & G. P. Youmans, *J. Bact.*, November, 1947, 54: 563.—(F. G. Petrlik)

**Promin in Experimental Tuberculosis.**—Eight groups of guinea pigs, consisting of 12 animals each, were utilized. Each animal was inoculated with 0.1 mg. of the human type of tubercle bacilli (H37Rv). Twenty-six days later, treatment of seven of the groups was started; the eighth group remained untreated for control. One group received promin orally, five groups received variable doses of promin subcutaneously and one group received streptomycin. Treatment was continued for seventy-six days and the experiment was terminated 102 days after the animals had been inoculated with the bacilli. Results indicated that promin given subcutaneously to tuberculous guinea pigs is fully as effective in its antituberculosis action as the same dose of promin given orally. The parenteral administration of promin did not, in guinea pigs, preclude the development of blood dyscrasia.—*Promin in Experimental Tuberculosis: Antituberculosis Effects of Sodium P, P'-Diaminodiphenylsulfone-N, N'-dioxetose Sulfonate (Promin) Administered Subcutaneously (A Preliminary Report)*, W. H. Feldman, A. G. Karlson & H. C. Hinshaw, *Proc. Staff Meet., Mayo Clin.*, March 8, 1948, 23: 118.—(P. Q. Edwards)

**Effect of Penicillin on Tubercle Bacillus.**—A virulent strain of tubercle bacillus, H37Rv, undergoes partial lysis in the presence of high concentrations of penicillin. Small inocula of tubercle bacilli are highly susceptible to concentrations of penicillin as low as 1 unit per cc. in the Tween-albumin medium, whereas 100 units per cc. causes no inhibition of growth in the oleic acid albumin medium. Preliminary experiments indicate that, in both the solid and liquid oleic acid albumin medium, penicillin in concentrations of 50 to 100 units per cc. may prove a valuable adjunct in culturing tubercle bacilli from contaminated materials.—*Effect of Penicillin on the Tubercle Bacillus in vitro*, W. M. M. Kirby & R. J. Dubos, *Proc. Soc. Exper. Biol. & Med.*, October, 1947, 66: 120.—(F. B. Seibert)

**Enhancement of Penicillin Blood Levels.**—This report illustrates the capacity of orally administered caronamide ("Staticin"—Sharp and Dohme, Inc.) to effectively increase penicillin blood levels in a group of patients where excessively high levels are essential for cure, i.e., subacute bacterial endocarditis. It has been shown that the excretion of penicillin by the renal tubular transport mechanism could be physiologically inhibited by caronamide. It is thought that the basis for this effect is one of competition between penicillin, which is excreted by the tubules, and caronamide, which is essentially refractory to excretion by that means. Caronamide was given orally in 2 or 3 gm. doses every four hours and the penicillin was administered intravenously with heparin. Accepting the dosage of 3 gm. every four hours as standard, the minimum increase over control blood levels was twofold and the maximum increase was sevenfold. No side effects of any consequence were noted.—*Enhancement of Penicillin Blood Levels following Oral Administration of Caronamide*, L. Loewe, H. B. Eiber, E. Altur-Werber, *Science*, November 21, 1947, 106: 494.—(E. A. Rouff)

**Coupled Sulphanilamide Derivatives.**—The sulphonamides examined were sulphanilamide, sulphapyridine, sulphathiazole, and sulphamethylthiazole. They were coupled to 2-methyl-1,4 naphthoquinone. These were dissolved in various concentrations in Löwenstein medium. Human tubercle bacilli strain No. 1354 in suspensions of 0.05 ml. containing 30 to 60 bacilli were employed for inoculation. Tubes were incubated at 37° C. All four sulphanilamides have a bacteriostatic effect; sulphathiazole and sulphamethylthiazole were most effective. The coupled compounds were the less effective. After serial subculturing it was shown that the sensitivity to the respective drugs was not changed. In the presence of sulphathiazolemethyl-naphthoquinone, the bacilli became longer and broader, were more diphtheroid, were colored more intensively, and contained greater amounts of nonacid-fast material. Under the electron microscope, it was seen that the bacilli were less dense and

characterised by clubbed ends and smaller granules. They were much broader, and the central denser part was surrounded by a wide, capsule-like external zone. These changes appeared to be of an involutionary nature. These experiments seem to support the conception that the compounds of methyl-naphthoquinone play a special role in the development of the morphological changes.—*The Effect on Tubercle Bacilli of Sulphanilamide Derivatives Coupled to Methyl-Naphthoquinone*, A. Grönwall & B. Zetterberg, *Upsala läkaref. förh.*, June 30, 1947, p. 199.—(R. W. Clarke)

#### **Para-Aminosalicyclic Acid in Tuberculosis.**

—Of a series of benzoic and salicyclic acid derivatives, para-aminosalicyclic acid was found to have the most active bacteriostatic action on tubercle bacilli. It is relatively nontoxic to animals. The optimum dosage for humans is thought to be 80 to 140 gm. per week, given orally. A total of 19 cases of tuberculosis were treated. All had pulmonary involvement, but only 6 were treated for those lesions *per se*. In the pulmonary series, all of which were active cases, the temperature and sedimentation rate fell within a few days. This improvement was maintained unless treatment was stopped. More slowly, there appeared a fall in pulse rate, an increase in weight and a decrease in the amount of sputum. There was roentgenographic improvement, particularly noteworthy being a decrease in the size of cavities. In one case of renal tuberculosis, no tubercle bacilli could be found in the urine after the twelfth day; by the eleventh week, the urine was free of albumen, pus and blood. In one case of tuberculous meningitis, oral medication was supplemented by 2 intrathecal injections each of 0.5 gm. of the drug in 5 per cent solution. The meningitic symptoms improved but the patient died of pulmonary tuberculosis. In one case of intestinal tuberculosis, there was symptomatic improvement. In one case treated by Monaldi drainage, introduction of the drug into the cavity resulted in diminution of the amount of discharge. In 9 cases of tuberculous empyema, including 3 with ex-

ternal sinuses, the oral medication was supplemented by weekly intrapleural administration of 1.5 to 3.0 gm. of the drug as a 10 per cent solution in distilled water. This treatment gave rapid and striking results.—*Para-Aminosalicylic Acid in Tuberculosis*, T. G. Dempsey & M. H. Logg, *Lancet*, December 15, 1947, 2: 871.—(A. G. Cohen)

**Tuberculostatic Action of Para-Aminosalicylic Acid.**—Lehman found that PAS was bacteriostatic in a concentration of 0.15 mg. per 100 ml. for BCG, that it exerted a favorable effect on clinical tuberculosis and that some retardation of experimental tuberculosis of guinea pigs could be effected after seven days of treatment with PAS. Youmans reported that PAS was highly bacteriostatic for 12 virulent strains of human type tubercle bacilli and exerted a suppressive action on experimental tuberculosis in mice. The present paper deals with further work on the tuberculostatic activity of p-aminosalicylic acid both *in vitro* and *in vivo*. This was tested *in vitro* by determining the least amount which would completely inhibit the subsurface growth of 0.01 mg. of tubercle bacilli per ml. of synthetic medium with and without 10 per cent bovine serum. The human type strains had been isolated within the preceding year and a half, with the exception of the standard H37Rv strain. In addition one stock bovine and one avian strain, as well as the avirulent rapidly growing strain no. 607, were used. Six of the human type strains were streptomycin-resistant. The effect of PAS *in vivo* was determined by infecting mice intravenously with 0.1 mg. of the H37Rv strain. PAS was incorporated in the desired concentration in the mouse diet. The mice were fed the diets containing PAS for twenty-eight days, starting the day before infection with tubercle bacilli. The results show that all of the strains except no. 607 were inhibited by very low concentrations of PAS. There was no significant difference between the results obtained with the streptomycin-sensitive and resistant strains. The avian strain seemed to be slightly more resistant to the bacteriostatic activity of PAS. The bacteriostatic activity

was partially reversed by para-aminobenzoic acid but was not reversed by sodium salicylate. The bacteriostatic activity of PAS was inversely proportional to the number of organisms present in the medium. Thirteen derivatives of PAS and salicylic acid were found to be much less tuberculostatic than PAS. Experimental tuberculosis of mice was suppressed by para-aminosalicylic acid when it was administered in the diet in 1 and 2 per cent concentrations. Under the conditions of the experiment 4 per cent PAS was highly toxic for mice. PAS and streptomycin when administered to mice simultaneously appeared to exert a suppressive effect on the tuberculous process greater than that of either substance alone. As the effect appears to be no more than additive, the implications in the treatment of clinical tuberculosis are obvious.—*The Tuberculostatic Action of Para-Aminosalicylic Acid*, G. P. Youmans, G. W. Raleigh & A. S. Youmans, *J. Bact.*, October, 1947, 54: 409.—(F. G. Petrik)

**Tuberculostatic Action of Alicyclic Compound Derivatives.**—The 3-n-amylicyclopentane-carboxylic acid mono-ester of sodium  $\beta$ -glycerophosphate was found to be half as effective as the 3-n-amylicyclopentane-carboxylic acid di-ester of sodium  $\beta$ -glycerophosphate in causing inhibition of growth of the tubercle bacillus (Strain A 27) *in vitro*, as well as in its tuberculostatic effect on the chorio-allantoic membrane of the chick embryo. Both substances were similar to the parent substance, sodium 3-n-amylicyclopentane-carboxylate, in their toxicity for the chick embryo. In white mice, all 3 compounds had a narcotic effect and produced hemorrhages at the site of injection.—*Tuberculostatic Action of Two Derivatives of the Alicyclic Compound, 3-n-Amylicyclopentane-Carboxylic Acid*, E. W. Emmart, *Proc. Soc., Exper. Biol. & Med.*, June, 1947, 65: 156.—(F. B. Seibert)

**Chemotherapy of Experimental Tuberculosis.**—A new class of highly tuberculostatic agents of low toxicity is described. This group comprises many 2,6-substituted derivatives of benzothiazole. Several of these

derivatives are active therapeutic agents in guinea pig tuberculosis. Structure-activity relations and possible modes of action are discussed.—*Chemotherapy of Experimental Tuberculosis with Benzothiazole Derivatives*, B. L. Freedlander & F. A. French, *Proc. Soc. Exper. Biol. & Med.*, November, 1947, 66: 362.—(F. B. Seibert)

**Chemotherapy in Tuberculosis.**—Using the medium of Dubos and Davis, 19 compounds

were tested *in vitro*. Only 4 showed sufficient activity to warrant further investigation. Compound 2-butoxy-5-amino-pyridine sodium formaldehyde bisulfite was found to be ineffective in the treatment of experimental tuberculosis in mice and guinea pigs.—*Chemotherapy of Tuberculosis: III. In vitro and in vivo Activities of Various Compounds*, C. J. Duca, R. D. Williams, & J. V. Scudi, *Proc. Soc. Exper. Biol. & Med.*, February, 1948, 67: 159.—(F. B. Seibert)





planned. Hence, as far as these particular antibiotics are concerned, the present paper will consider only *in vitro* studies.

#### IN VITRO STUDIES

In recognition of the marked effects that test conditions have on the activities of both streptomycin (8) and mannosidostreptomycin (2), efforts have been made to establish rigorous conditions of standardization of all *in vitro* tests.

TABLE 1

*In vitro* activities of pure streptomycins against various organisms

| TEST ORGANISM   | MINIMAL INHIBITING CONCENTRATION* |                      |                        |                              |
|---|-----------------------------------|----------------------|------------------------|------------------------------|
|   | Streptomycin                      | Dihydro-streptomycin | Mannosido-streptomycin | Dihydromannosidostreptomycin |
|   | μg/ml.                            | μg/ml.               | μg/ml.                 | μg/ml.                       |
| <i>Klebsiella pneumoniae</i> (ATCC 9997) .....        | 1.76                              | 1.76                 | 6.39                   | 6.59                         |
| <i>Aerobacter aerogenes</i> (ATCC 129) .....          | 2.71                              | 3.27                 | 10.8                   | 11.1                         |
| <i>Escherichia coli</i> , D 56 .....                  | 6.05                              | 6.79                 | 24.8                   | 23.8                         |
| <i>Salmonella schottmüller</i> i .....                | 10.1                              | 36.5                 | 14.3                   | 14.4                         |
| <i>Salmonella typhosa</i> .....                       | 12.2                              | 51.0                 | 12.4                   | 12.9                         |
| <i>Staphylococcus aureus</i> 209P .....               | 0.828                             | 1.39                 | 5.64                   | 7.77                         |
| <i>Brucella abortus</i> (Huddleson 1119 avirulent) .. | 0.816                             | 0.738                | 2.93                   | 2.53                         |
| <i>Mycobacterium tuberculosis</i>                     |                                   |                      |                        |                              |
| <i>Streptococcus pyogenes</i> , C203 .....            | 11.7                              | 15.9                 | 82.9                   | 87.9                         |
| H37Rv .....   | 2.0                               | 2.2                  | 5.5                    | 6.5                          |
| Ravenel .....   | 0.58                              | 0.62                 | 2.5                    | 2.2                          |
| BCG .....   | 0.52                              | 0.55                 | 1.9                    | 1.7                          |
| N.† .....   | 0.54                              | 0.56                 | 2.5                    | 2.1                          |
| T.† .....   | 0.55                              | 0.54                 | 2.2                    | 2.0                          |
| P.† .....   | 0.62                              | 0.85                 | 2.3                    | 2.2                          |
| O'D.† .....   | 0.63                              | 0.75                 | 2.3                    | 2.6                          |
| K.† .....   | 1.0                               | 1.7                  | 3.9                    | 3.9                          |

\* All figures are given in terms of weight of the trihydrochlorides. On the basis of assays with *K. pneumoniae*, the streptomycin and dihydrostreptomycin would have an activity of 820 units per mg., the mannosidostreptomycin an activity of 236 units per mg., and the dihydromannosidostreptomycin 228 units per mg.

† Strains of *M. tuberculosis* freshly isolated from human cases.

A uniform preparation of yeast beef broth was employed as the test medium for 11a test organisms which grow readily in it. (This group included the first seven species listed in table 1.) For the *Streptococcus pyogenes* (C203) 0.05 per cent bovine albumin-Frackin V was added to this same yeast beef broth. All strains of *M. tuberculosis* were tested in a modified Kirchner's medium (2) containing Tween 80 and bovine serum albumin, fraction V. The test procedure for all organisms other than the various strains of *M. tuberculosis* was essentially that described earlier (9). Precise end points with the latter organisms cannot be obtained in a broth dilution test having 12 per cent dilution steps. Therefore, for all strains of this species the volumes of antibiotic solution were added to give 25 per cent dilution steps.

For each species or strain of organism, therefore, test conditions were uniform for all four streptomycins, and horizontal comparisons in table 1 are permissible.

Conversely, in attempting to make perpendicular comparisons, that is comparison of the sensitivity of one species with another, due consideration must be taken of any differences in test conditions. The test medium used for the *Mycobacteria*, for instance, is of relatively simple synthetic composition and undoubtedly contains less substances capable of interfering with streptomycin action than does yeast beef broth.

As has been reported previously (1), against some organisms dihydrostreptomycin is less active than streptomycin. In no case is it more active. Marked examples of lesser activity shown in table 1 are *Salmonella schottmülleri* and *Salmonella typhosa*. These two species are remarkable from another standpoint also. For all other species tested mannosidostreptomycin has only a fraction of the activity of streptomycin, while for the latter two species the two compounds are essentially equal in activity.

It will be noted that for most of the strains of *M. tuberculosis* tested there is little difference between the *in vitro* activities of streptomycin and its dihydro derivative. The one exception is the strain labeled "K" where the latter compound, while still having an activity of high order, is nevertheless less active than the parent compound. All figures in the table are based on repeated determinations, ranging from a minimum of 8 tests to as many as 25 depending upon how well replicates checked. In the case of the "K" strain 18 to 22 tests were run on each compound and statistical analysis of the results indicates that the difference between the activities of the two compounds is highly significant.

In comparing mannosidostreptomycin with its dihydro derivative it is interesting that no case has been found as yet comparable to the differences in response shown by *S. schottmülleri* and *S. typhosa* to streptomycin and dihydrostreptomycin. *Staphylococcus aureus* 209P is apparently slightly less sensitive to dihydromannosidostreptomycin, but for all other organisms tested the two closely related compounds are equally active. The possibility was recognized early that dihydrostreptomycin might be converted to streptomycin before acting as an antibiotic (1) but, although confirmation of this has been claimed (10), clear-cut proof has never been obtained and all the evidence in fact has been against such a conversion. In this connection, the observation of Tompsett (11) that individuals sensitive to streptomycin are not sensitive to equivalent amounts of dihydrostreptomycin would appear to be significant. In the present instance, if conversion occurs, it is difficult to explain why dihydromannosidostreptomycin is as active as mannosidostreptomycin against *S. typhosa* and *S. schottmülleri*, while dihydrostreptomycin is so much less active for these two organisms than is its parent compound.

#### IN VIVO STUDIES

As already indicated, it has not yet been possible to complete *in vivo* studies with mannosidostreptomycin and dihydromannosidostreptomycin. The present report will therefore limit itself to certain preliminary results obtained with pure streptomycin and dihydrostreptomycin.



*Absorption and Excretion of Pure Streptomycin Trihydrochloride and its Dihydro Derivative in Mice*

In an earlier paper (1) it was reported that the absorption-excretion rates of streptomycin and dihydrostreptomycin are very similar, at least for partially purified materials. This has now been confirmed with the pure entities, as may be seen in figure 1. A single subcutaneous dose of 2.5 mg. of pure trihydrochloride (approximately 102,000 units per kg.) was administered in each case

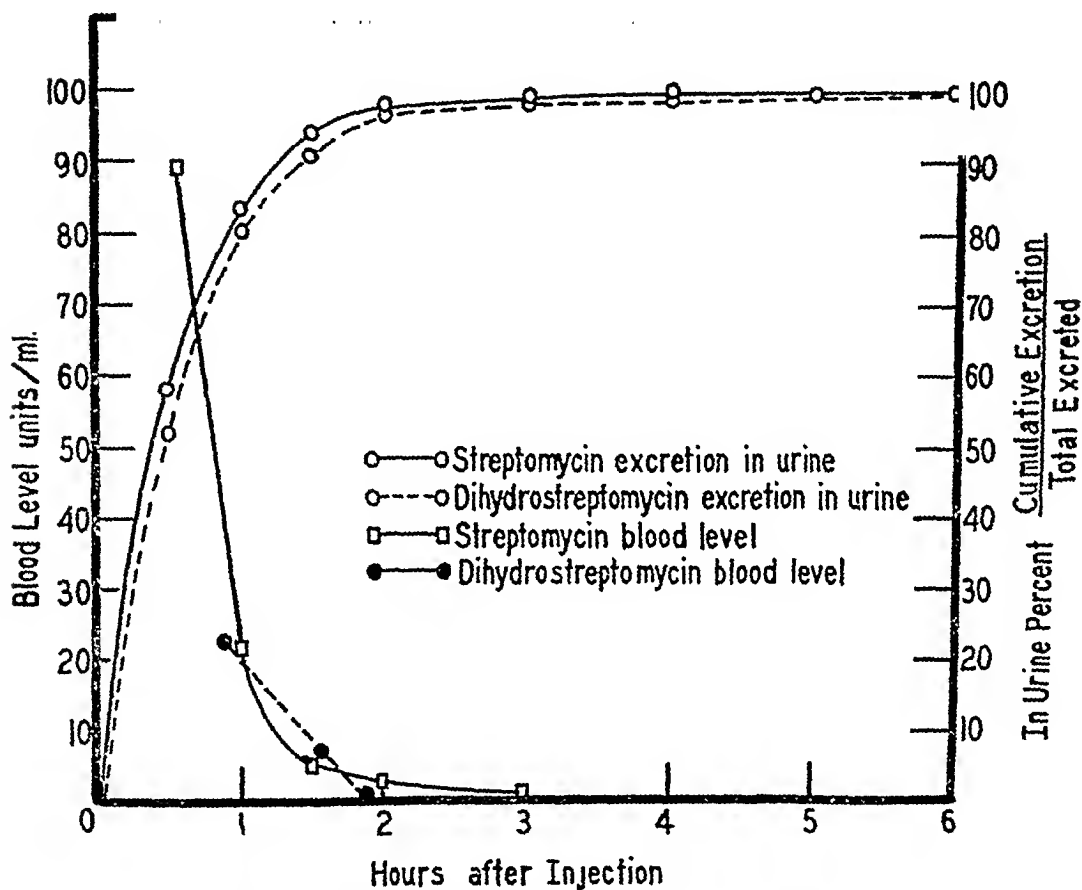


FIG. 1. Comparison of absorption excretion of pure trihydrochlorides of streptomycin and dihydrostreptomycin in mice.

and blood and urine handled in the manner described previously (1). Overall recovery of the antibiotics in the urine was between 30 and 40 per cent of the dose administered which is within the broad range of recovery reported earlier (1, 12).

In the case of streptomycin the first blood samples were obtained within one half hour after injection and the pooled serum sample showed an activity of almost 90 units per ml. One hour after injection the serum level had dropped to approximately 21 units per ml. The first dihydrostreptomycin serum samples were not obtained until fifty minutes after injection and contained 22 units per

ml., which agrees with the one hour figure for streptomycin. The one and one-half hour serum samples in both cases contained approximately 6 units of antibiotic per ml. and during the next hour dropped to 2 or less units per ml.

Of the total amounts of antibiotics recovered in the urine, in both cases 52 to 58 per cent appeared during the first half hour, 80 to 84 per cent in one hour, and 91 to 94 per cent within one and one-half hours.

### *Acute Toxicity in Mice*

The acute toxicities of pure streptomycin trihydrochloride and the corresponding dihydro compound, as shown by subcutaneous inoculation into mice, are very similar. Both cause severe shock and cyanosis at doses of 1,500 mg. per kg. (1,230,000 units per kg.) or more and a high percentage of deaths at doses slightly beyond this point. A typical experiment showing this is given in table

TABLE 2  
Comparison of acute toxicities of the trihydrochlorides of pure streptomycin and dihydrostreptomycin\*

| COMPOUND                              | DOSE†<br>MG./KG. | IMMEDIATE EFFECTS        | DEATHS<br>WITHIN<br>24 HOURS |
|---------------------------------------|------------------|--------------------------|------------------------------|
| Streptomycin trihydrochloride.....    | 842              | Slight to severe shock   | 1/10‡                        |
| Streptomycin trihydrochloride.....    | 1,000            | Severe shock             | 1/15                         |
| Streptomycin trihydrochloride.....    | 1,530            | Severe shock             | 12/15                        |
| Streptomycin trihydrochloride.....    | 2,000            | Severe shock             | 13/15                        |
| Dihydrostreptomycin trihydrochloride. | 1,005            | Slight to moderate shock | 2/20                         |
| Dihydrostreptomycin trihydrochloride. | 1,500            | Severe shock             | 5/20                         |
| Dihydrostreptomycin trihydrochloride. | 1,923            | Severe shock             | 16/20                        |

\* Dose: 0.5 ml. of given solution, subcutaneously.

† To convert to units per kg. multiply by 820.

‡ Number dying/number injected.

2. Here the  $L_{50}$  of the trihydrochloride of streptomycin was  $1440 \pm 116$  mg. per kg., and that of dihydrostreptomycin was  $1600 \pm 108$  mg. per kg. (equivalent to 1,180,000 and 1,310,000 units per kg., respectively). In an earlier paper (1) it has been shown that the acute intravenous toxicity of impure preparations of the two antibiotics in mice is essentially similar.

### *Comparative Therapeutic Action in Experimental Tuberculosis in Mice*

A complete description of the standardized experimental infection of mice with *M. tuberculosis* (Ravenel) employed in this laboratory will appear in a later publication (13). For the present let it suffice to say that with properly chosen strain of organism and mouse it has been possible to obtain remarkably uniform results with this infection. In the experiment described here the doses of antibiotics employed were chosen, on the basis of previous experience, so that the lowest level of streptomycin used would give a therapeutic response just perceptible within a thirty day period. Only at such minimal levels, it was felt, would differences between streptomycin and dihydrostreptomycin be noted.

In a typical experiment a standard strain of mice CF 1 were inoculated intravenously with a standardized inoculum of *M. tuberculosis* (Ravenel) grown in a simple medium containing Tween 80 and albumin. On the day of inoculation, treatment was started with streptomycin or dihydrostreptomycin, the mice receiving a single subcutaneous injection daily for twenty-one days. A group of untreated mice, and four groups treated with p-aminosalicylic acid at four levels in the diet for twenty-one days, were included for comparison. The results of this experiment are summarized in table 3.

TABLE 3

*Comparison of streptomycin and dihydrostreptomycin in treatment of experimental tuberculosis in the mouse*

| TREATMENT                   | NUMBER OF MICE | DEAD/TOTAL* | $t_{50}†$ | INCREASE IN $t_{50}$ , PER CENT |
|-----------------------------|----------------|-------------|-----------|---------------------------------|
| None.....                   | 14             | 14/14       | 22.3      |                                 |
| <i>Streptomycin</i>         |                |             |           |                                 |
| 6,600 units/kg.....         | 10             | 10/10       | 26.0      | 16.6                            |
| 10,000 units/kg.....        | 10             | 10/10       | 28.0      | 25.8                            |
| 15,000 units/kg.....        | 10             | 7/10        | 33.0      | 47.5                            |
| 22,500 units/kg.....        | 10             | 2/10        | 35.0      | ≥57.0                           |
| <i>Dihydrostreptomycin</i>  |                |             |           |                                 |
| 6,600 units/kg.....         | 10             | 7/10        | 27.2      | 22.0                            |
| 10,000 units/kg.....        | 10             | 8/10        | 28.0      | 25.8                            |
| 15,000 units/kg.....        | 10             | 8/10        | 29.0      | 30.0                            |
| 22,500 units/kg.....        | 9              | 5/9         | 33.1      | 48.4                            |
| <i>P.A.S.</i>               |                |             |           |                                 |
| 0.2 per cent in diet.....   | 10             | 10/10       | 24.0      | 7.6                             |
| 0.375 per cent in diet..... | 10             | 10/10       | 25.0      | 11.7                            |
| 0.75 per cent in diet.....  | 10             | 10/10       | 28.0      | 25.8                            |
| 1.0 per cent in diet.....   | 10             | 7/10        | 30.0      | 35.0                            |

\* Based on mice dead on 34th day.

†  $t_{50}$  = Estimated 50 per cent survival time.

On the basis of prolongation of the 50 per cent survival time ( $t_{50}$ ), P.A.S. at 0.75 per cent in the diet yielded the same response as streptomycin and dihydrostreptomycin given in a single, subcutaneous, injection daily at 10,000 units per kg. In the present test at 6,600 and 10,000 units per kg. daily, streptomycin and dihydrostreptomycin were equivalent to each other. At 15,000 and 22,500 units per kg. the prolongation of life in the case of streptomycin was slightly greater than that of dihydrostreptomycin, but in other similar tests the reverse of this picture has been found. A consideration of all the available data indicates no difference in the effect of streptomycin and dihydrostreptomycin on infections with the Ravenel strain in mice.

The therapeutic efficacies of streptomycin and dihydrostreptomycin have also been compared in standardized experimental acute infections in mice. Thus, against approximately 1,000 lethal doses of *S. schottmülleri*, streptomycin gave a  $CD_{50}$  of 11,320 units per kg. and dihydrostreptomycin a  $CD_{50}$  of 21,730 units

per kg. (based on 20 mice at each of 4 dose levels). Against approximately 500 lethal doses of *Streptococcus pyogenes* C-203, the  $CD_{50}$  for streptomycin was ca. 80,000 units per kg. while for the dihydro compound was 77,000 units per kg.

It is interesting to note that against *S. schottmülleri* infections in mice, dihydrostreptomycin was more effective, relative to streptomycin, than would be expected from *in vitro* data (table 1), where the latter was 3.6 times as active as the former against this organism.

#### DISCUSSION

The results of these further studies on different streptomycins and dihydrostreptomycins serve to confirm the essential similarities in the biological behavior of the dihydrostreptomycins to the streptomycins from which they have been derived. The similarities already established have been referred to in the introduction to the present paper. The present studies emphasize the fact that only in the *in vitro* tests have any significant differences been uncovered. As far as pathogens are concerned only the two gram negative bacteria, *S. schottmülleri* and *S. typhosa*, of those species studied so far have shown any marked difference in regard to their sensitivity to dihydrostreptomycin as compared to streptomycin itself. As pointed out, even with these organisms there is no difference when the sensitivity to mannosidostreptomycin and dihydromannosidostreptomycin is considered. Further studies on the absorption, excretion and acute toxicity of pure materials has shown how similar these are for dihydrostreptomycin and streptomycin itself. Finally, *in vivo* tests using a highly standardized tuberculosis infection in mice have not revealed significant differences in response when the variation between doses used has been in 50 per cent increments. In none of these laboratory studies has dihydrostreptomycin proved superior to streptomycin itself but from the results obtained it would seem probable that amongst those pathogenic organisms so far investigated, only members of the *Salmonella* group could be expected to show appreciable difference in response to therapy with these two antibiotics.

#### SUMMARY

Pure preparations of streptomycin (streptomycin A), dihydrostreptomycin (dihydrostreptomycin A), mannosidostreptomycin (streptomycin B), and dihydromannosidostreptomycin (dihydrostreptomycin B) have been compared. In accord with previously published data, it has been found that dihydrostreptomycin has biological properties closely resembling those shown by the parent streptomycin species. Only with the *in vitro* test, and there particularly with members of the genus *Salmonella*, have any striking differences been found between dihydrostreptomycin and streptomycin itself. It seems probable that *in vivo* differences between dihydrostreptomycin and streptomycin would be found only with *Salmonella* infections of those pathogens so far tested.

*In vivo* tests using a highly standardized tuberculosis infection in mice have not revealed significant differences in response when the variation between the doses used has been in 50 per cent increments.

## SUMARIO

*Nuevos Estudios sobre la Dihidroestreptomicina*

Al comparar preparaciones puras de estreptomicina (estreptomicina A), dihidroestreptomicina (dihidroestreptomicina A), manosidoestreptomicina (estreptomicina B) y dihidromanosidoestreptomicina (dihidroestreptomicina B), descubrióse que, de acuerdo con datos previamente publicados, la dihidroestreptomicina posee propiedades biológicas íntimamente parecidas a las reveladas por la especie matriz: la estreptomicina. Sólo en los ensayos *in vitro*, y en ellos en particular con los miembros del género *Salmonella*, observáronse diferencias notables entre la dihidroestreptomicina y la estreptomicina misma. Parece probable que, entre los gérmenes patógenos comprobados hasta ahora, sólo se descubrirían diferencias *in vivo* entre las dos drogas en las infecciones por *Salmonella*.

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# AN EXPERIMENTAL EVALUATION OF DIHYDROSTREPTOMYCIN<sup>1</sup>

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## INTRODUCTION

Despite the increased understanding of the proper therapeutic use of streptomycin in tuberculosis and the high purity of the preparations now available, the incidence of disturbances of vestibular function in patients receiving long courses of treatment is still sufficiently great to warrant a continuing search for equally effective but less neurotoxic agents. Dihydrostreptomycin, prepared by the catalytic hydrogenation of streptomycin and first described by Peck, Hoffhine and Folkers (1) and by Bartz *et al.* (3), appears to fulfill these requirements. The present studies show that its antimicrobial efficacy against *M. tuberculosis* is equal to that of streptomycin, while its neurotoxic action in animals is significantly less than that of the parent substance.

## OBSERVATIONS

**Materials:** Three samples of crystalline dihydrostreptomycin<sup>2</sup> and two of crystalline streptomycin calcium chloride complex were used in this investigation. The specifications of the various samples<sup>3</sup> are shown in table 1.

**Efficacy:** Dihydrostreptomycin and streptomycin showed closely comparable activity on a weight for weight basis against the tubercle bacillus of both human (H37Rv) and avian types *in vitro*. *In vivo* they were equally effective against avian tuberculosis in chicks. Details of these studies will be reported elsewhere. No substantial differences were observed in mice infected with *K. pneumoniae*, *D. pneumoniae* I-37, *Staph. aureus* SM or *E. typhosa*. (See also 2, 3).

**Bacterial resistance:** Cultures of tubercle bacilli, resistant to streptomycin, were also resistant to dihydrostreptomycin. Mice infected with streptomycin resistant cultures of *S. Schottmülleri* could not be protected by either streptomycin or dihydrostreptomycin.

## Neurotoxicity

The toxic actions of dihydrostreptomycin and streptomycin on the nervous system were compared in cats (4, 5, 6). The drugs were given once daily by subcutaneous injection: dihydrostreptomycin in doses equivalent to 38, 77, 155 and 200 mg. of base per kg. of body weight, and streptomycin in doses equivalent to 25, 50, 100 and 200 mg. of base per kg. The amounts of base were calculated from the molecular weights of the compounds and the purity of the preparations. Groups of 4 animals were employed at all dose levels but one, where 5 animals were used. Each cat was observed daily, and the number of days required for

<sup>1</sup> From the Merck Institute for Therapeutic Research, Rahway, New Jersey.

<sup>2</sup> We are indebted to Dr. F. J. Wolf for preparing the crystalline dihydrostreptomycin used in this investigation.

<sup>3</sup> All were obtained from the Research Laboratories of Merck & Co., Inc., Rahway, New Jersey.

the development of ataxia, head oscillations and defective righting reflexes, the characteristic signs of disturbed vestibular function, was noted.

TABLE 1

| LOT   | PURITY ESTIMATED<br>(BY ROTATION) | STREPTOMYCIN CONTENT<br>(BY MALTOL ASSAY) | I.V. TOXICITY<br>LD <sub>50</sub> —MICE |
|---|-----------------------------------|---|---|
| Dihydrostreptomycin trihydrochloride (crystalline)  |                                   |   |   |
| 7R3724  | 92 per cent                       | 2.5 mcg./mg. (0.3 per cent)               | 4.45 mg.                                |
| SR2514  | 95 per cent                       | 22 mcg./mg. (2.5 per cent)                | 3.52 mg.                                |
| 8R2961  | 95 per cent                       | 4 mcg./mg. (0.5 per cent)                 | 3.52 mg.                                |
| Streptomycin calcium chloride complex (crystalline) |                                   |   |   |
| 7R9694  | 87.5 per cent*                    | 675 mcg./mg.                              | 5.25 mg.                                |
| 8R1296  | 87.5 per cent*                    | 680 mcg./mg.                              | 5.26 mg.                                |

\* > 95 per cent after allowance for volatile constituents.

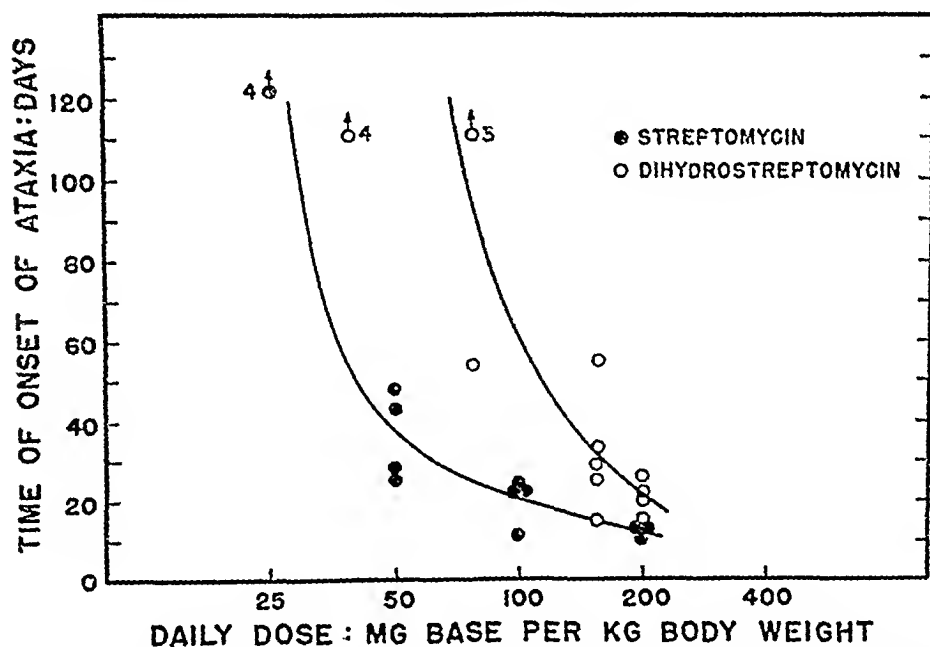


FIG. 1. Time of appearance of ataxia in cats treated with dihydrostreptomycin or with streptomycin. Each point represents one animal, except where shown otherwise by numerals. Arrows indicate absence of neurotoxic effects.

In figure 1 the number of days of treatment required to produce ataxia is plotted as a function of the size of the dose employed. It is apparent from this graph that at all of the dose levels which produced intoxication, the onset of ataxia was longer delayed with dihydrostreptomycin than with streptomycin. Neither streptomycin in a dose of 25 mg. per kg., nor dihydrostreptomycin in a

dose of 38 mg. per kg., produced any ataxia or other sign of vestibular disturbance during periods of treatment lasting 122 and 111 days respectively. All 4 cats receiving streptomycin in doses of 50 mg. per kg. became ataxic within 25 to 48 days, while only one of the cats receiving dihydrostreptomycin in doses of 77 mg. per kg. was ataxic after 51 days and 3 still had a normal gait after 110 days of treatment.

In larger doses dihydrostreptomycin produced vestibular disturbance in all animals tested, but its onset was significantly delayed as compared with that caused by streptomycin.

In the animals receiving doses of 200 mg. per kg. (table 2) a more intensive study of the vestibular defect was made by electrical recording of nystagmus, a

TABLE 2

| CAT NUMBER   | ONSET OF ATAXIA,<br>DAYS | MAXIMUM SEVERITY | WEIGHT (GM.) |       |
|--|--------------------------|------------------|--------------|-------|
|  |                          |                  | Initial      | Final |
| Dihydrostreptomycin-3HCl SR2511—200 Mg/Kg/Day subcutaneously for 30 days       |                          |                  |              |       |
| 1,055  | 27                       | ++               | 2,375        | 2,450 |
| 1,056  | 23                       | +                | 2,680        | 2,660 |
| 1,059  | 16                       | +++              | 3,310        | 3,385 |
| 1,070  | 21                       | +                | 2,475        | 2,050 |
| Average .....  | 22                       |                  |              |       |
| Streptomycin-CaCl <sub>2</sub> SR1296—200 Mg/Kg/Day subcutaneously for 20 days |                          |                  |              |       |
| 1,013  | 12                       | +++              | 3,350        | 3,125 |
| 1,067  | 14                       | +++              | 2,815        | 2,240 |
| 1,068  | 14                       | +++              | 2,525        | 2,215 |
| 1,071  | 13                       | ++++             | 2,565        | 2,060 |
| Average .....  | 13                       |                  |              |       |

procedure which permitted a quantitative evaluation of the loss of response occasioned by the drug. The individual cats were rotated on a motor-driven turntable at 60 r.p.m. for 30 sec. in the clockwise direction; then, after 2 minutes of rest, for 30 sec. counterclockwise. Horizontal nystagmus was recorded continuously during and after rotation by means of a Grass ink-writing oscillograph registering the variation in corneo-retinal potential between two solder-disc electrodes in contact with the shaved skin at the outer canthi (5). In order to eliminate optokinetic nystagmus, the head was covered with a cardboard housing, which served to prevent the cat from seeing the apparent motion of surrounding objects but did not interfere with free movement of the eyes as a blindfold had been found to do.

The average number of cycles of nystagmus during a 30 sec. period of rotation in each direction was taken as a measure of the response of the vestibular system.



Each curve of figure 2 represents the changes in this response in a single animal as recorded at various times during treatment with the two drugs. In addition, a curve for a normal control animal is presented to indicate the amount of decrease in the response with repeated spinning alone. From these curves it is apparent that loss of nystagmus, like ataxia, occurs earlier in the course of treatment with streptomycin than with equivalent doses of dihydrostreptomycin. It should be noted also that in only one cat was the loss of nystagmus after 30 days of treatment with dihydrostreptomycin as great as it was in all 4 cats of the other groups after 20 days of treatment with streptomycin. The test with streptomycin was stopped after 20 days because the intoxication was so severe

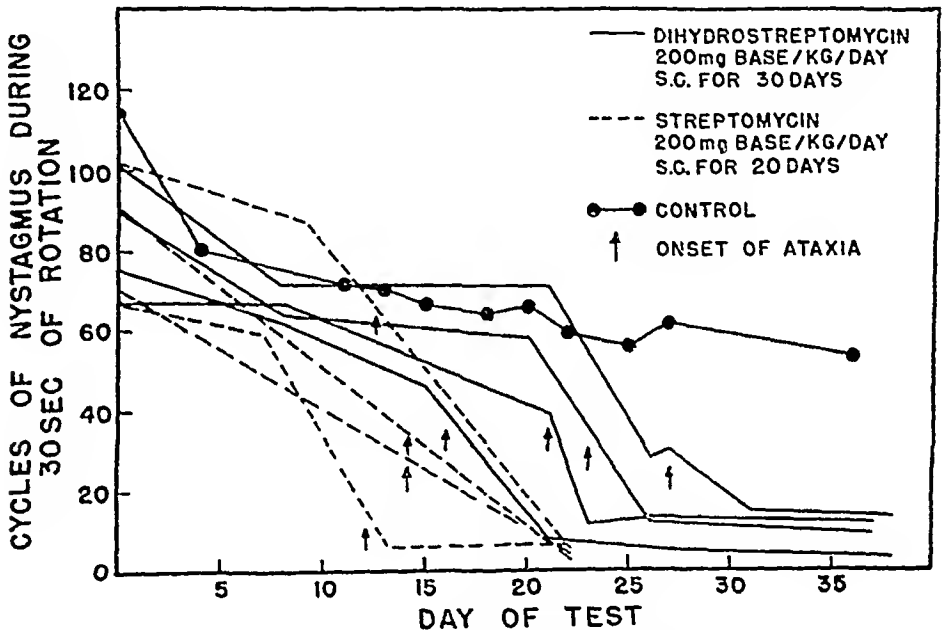


FIG. 2. Loss of vestibular nystagmus in cats treated with dihydrostreptomycin or with streptomycin. Control curve shows effect of repeated tests in untreated normal cat. Rotation for 30 sec. at 60 r.p.m. with eyes covered.

that the cats were rapidly losing weight. In contrast, the animals treated with dihydrostreptomycin maintained or gained weight during the 30 day treatment.

Two dogs treated with streptomycin, in doses of 200 mg. per kg. daily, showed an ataxic gait on the twelfth and fourteenth days, respectively, while 2 dogs receiving equal doses of dihydrostreptomycin showed no evidence of a neurotoxic effect during 18 days of treatment.

#### *Other Toxic Effects in Dogs and Monkeys*

In order to compare other possible toxic effects of the two drugs, biochemical and hematological studies were carried out in 6 dogs and 6 monkeys. Two animals of each species received streptomycin, 2 were given dihydrostreptomycin,

and 2 served as untreated controls. The drugs were given twice daily by subcutaneous injection of 200 mg. of base per kg. divided into two equal doses. The concentration of the solution used was 400 mg. of base per ml. Treatment of the dogs was carried out for 18 days, and of the monkeys for 5 days. Ten to 12 days after the last injection the animals were sacrificed for pathologic study.

*Weight changes:* The body weights of the monkeys remained relatively constant during the period of treatment. Slight but probably insignificant decreases in weight of 5.8 per cent and 3.3 per cent were noted 10 days later in animals injected with streptomycin and dihydrostreptomycin respectively. One dog given streptomycin and both dogs given dihydrostreptomycin showed weight losses of about 1 kg. by the eighteenth day. Although both dihydrostreptomycin-treated animals were regaining weight 10 days after the last injection, the streptomycin-treated dog showed a further weight loss at this time.

*Biochemical determinations:* No evidence of altered liver or kidney function was found in any of the following determinations which were made on blood specimens from both dogs and monkeys: bromsulfalein retention, nonprotein nitrogen, sugar, cholesterol ester, total cholesterol; serum phosphatase (alkaline) and calcium. Likewise, determinations of the pH and specific gravity of the urine and examinations for blood, protein, and urobilinogen revealed no abnormal findings (7). Decreases in serum protein of 0.2 to 0.25 gm. per cent were found in the treated dogs and of 0.5 to 0.7 gm. per cent in the treated monkeys, changes presumably associated with decreases in body weight. In dogs given streptomycin, the albumin-globulin ratio decreased from 2.25 to 1.2; in monkeys from 2.5 to 1.2. These changes are not beyond the normal range. In 3 of the 4 treated monkeys an increase in plasma fibrinogen occurred, presumably because of tissue damage at the site of injection.

*Hematological effects:* The monkeys showed no significant changes in erythrocyte count, leukocyte count, hemoglobin, hematocrit, erythrocyte sedimentation rate or prothrombin time as a result of the drug treatment. Definite changes occurred in only one dog, which developed a leukocytosis (24,760 cells per cu. mm.) and a slight normocytic anemia after two weeks of treatment with streptomycin. Ten days after the last injection the total leukocyte count had returned to normal, but the anemia was still evident.

*Urinalysis:* Microscopic examination of the urine sediments revealed no abnormalities in any of the monkeys or dogs.

*Pathological effects:* The incidence and extent of ulceration and induration at the injection sites were greater in dogs and monkeys given streptomycin than in those treated with dihydrostreptomycin.

Gross examination at autopsy revealed no organ changes in treated monkeys or dogs. The weights of liver, kidney, spleen, heart, pituitary, thyroid and adrenal glands were comparable in treated and control animals.

Microscopic examination of hematoxylin-eosin stained sections from the dogs and monkeys revealed no pathological changes in kidney, liver, heart, lung, pancreas, spleen, lymph node, adrenal gland, thyroid gland, pituitary gland, testis or representative sections of the gastro-intestinal tract. Sections of liver,

kidney and adrenal glands stained with Sudan IV showed no differences between animals treated with streptomycin or dihydrostreptomycin and the controls. These negative findings in liver and kidney are in contrast to those reported by Mushett and Martland (8) with less pure preparations of streptomycin.

Hyperplasia of the femoral bone marrow was observed in the streptomycin treated dog which had previously exhibited a slight, persistent anemia.

#### DISCUSSION

Dihydrostreptomycin and streptomycin appear to affect the nervous system in the same fashion. No qualitative distinctions have been noted in cats, the signs produced by the two drugs differing only in time of onset and in severity. Whether these quantitative differences in toxicity depend upon less rapid excretion of streptomycin or more ready access to the nervous system, or upon differences in metabolism of the two substances, cannot be answered at present. The significant fact is that, in the conversion of streptomycin to dihydrostreptomycin, the neurotoxic action has been reduced without sacrificing the antimicrobial efficacy. The two properties do not, therefore, appear to be indissolubly linked and presumably do not depend upon the same molecular configuration.

#### SUMMARY

1. Dihydrostreptomycin and streptomycin were closely comparable in antibacterial activity on a weight for weight basis against *M. tuberculosis* of human (H37Rv) and avian types *in vitro* and against the avian type in chicks.

2. No substantial differences in antibacterial activity of the two drugs were found against a variety of other pathogenic micro-organisms *in vitro* and *in vivo*.

3. Micro-organisms resistant to streptomycin are also resistant to dihydrostreptomycin.

4. The chronic neurotoxicity of dihydrostreptomycin in cats is less than that of streptomycin. When the two drugs are given to cats in doses containing equal weights of base, ataxia and loss of nystagmus appear later and are less severe with dihydrostreptomycin than with streptomycin.

5. Biochemical, hematological, and pathological studies revealed no significant evidence of other toxicity in dogs or monkeys treated with dihydrostreptomycin.

#### SUMARIO

##### *Valuación Experimental de la Dihidroestreptomicina*

1. La dihidroestreptomicina y la estreptomicina mostráronse netamente comparables en actividad antibacteriana, a base de peso por peso, contra los tipos humano (H37Rv) y aviario del *M. tuberculosis in vitro* y contra el tipo aviario en los pollos.

2. No se observaron diferencias sustanciales en la actividad antibacteriana de las dos drogas contra otros varios microbios patógenos, tanto *in vitro* como *in vivo*.

3. Los microorganismos resistentes a la estreptomicina también lo son a la dihidroestreptomicina.

4. La neurotoxicidad crónica de la dihidroestreptomicina en los gatos es menor que la de la estreptomicina. Cuando se administran las dos drogas a los gatos a dosis que contienen pesos iguales de la base, la ataxia y la pérdida del nistagmo se presentan más tarde y son menos intensas con la dihidroestreptomicina que con la estreptomicina.

5. Los estudios bioquímicos, hematológicos y patológicos no revelaron otros signos significativos de toxicidad en los perros y monos tratados con dihidroestreptomicina.

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# DIHYDROSTREPTOMYCIN: ITS EFFECT ON EXPERIMENTAL TUBERCULOSIS

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## INTRODUCTION

The conversion, by hydrogenation, of streptomycin trihydrochloride to dihydrostreptomycin trihydrochloride was announced in 1946 by Peck, Hoffhine and Folkers (1) and by Bartz, Controulis, Crooks and Rebstock (2). The hydrogenated product was found to be chemically distinctive, having increased stability. Unlike streptomycin, it was not inactivated by cysteine or by carbonyl reagents and did not yield maltol in the presence of alkali. These facts, together with the fact of its altered pharmacologic properties, recently determined by Edison and her co-workers (3), make it evident that dihydrostreptomycin is in reality a new antibacterial substance and one of potential merit. The biologic activity of dihydrostreptomycin against a variety of micro-organisms tested *in vitro* was qualitatively and quantitatively similar to that of streptomycin. For some bacteria the antibacterial activity of dihydrostreptomycin was inferior to that of the parent substance (2, 4). Activity *in vivo* of dihydrostreptomycin comparable to that of streptomycin was demonstrated in mice infected with *Salmonella schottmüller*, *Klebsiella pneumoniae*, *Diplococcus pneumoniae*, *Staphylococcus aureus* "S M" or *Eberthella typhosa*.

The relationship of dihydrostreptomycin to streptomycin and the high anti-tuberculosis potency of the parent substance naturally raises the question concerning the ability of dihydrostreptomycin to control or suppress tuberculous infections. Youmans (5) found dihydrostreptomycin and streptomycin of equal potency *in vitro* against the human strain of tubercle bacilli H37Rv. Edison and her co-workers (3) also found dihydrostreptomycin and streptomycin of comparable activity *in vitro* against the H37Rv strain and against *Mycobacterium tuberculosis avium*. In addition, Edison and her co-workers (3) observed that the hydrogenated compound was comparable in effectiveness against *Mycobacterium tuberculosis avium* infections in chicks. To obtain information regarding the therapeutic efficacy of dihydrostreptomycin against tuberculous disease in animals induced by a human strain of *Mycobacterium tuberculosis*, the following studies were done.<sup>3</sup>

## EXPERIMENTAL OBSERVATIONS

### EXPERIMENT I

#### Methods

The first experiment, initiated in March, 1947, concerned three groups of guinea pigs, each of which was inoculated subcutaneously with 0.001 mg. of tubercle bacilli, human

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<sup>3</sup> Since this paper was written, a report on dihydrostreptomycin in experimental tuberculosis by Freedlander and French (Dis. of Chest, November-December, 1947, 13, 70S) has come to our attention. They concluded that the therapeutic efficacy of dihydrostreptomycin was comparable to that of streptomycin.

strain H37Rv (streptomycin-sensitive). Forty-two days after inoculation the animals were divided into three groups as follows: group 1, untreated controls; group 2, treated once daily, each animal receiving subcutaneously 6 mg. of dihydrostreptomycin trihydrochloride<sup>4</sup>; group 3, treated once daily, each animal receiving streptomycin calcium chloride complex subcutaneously equivalent to 6 mg. of streptomycin base<sup>5</sup>.

The experiment continued until the animals had received treatment for 119 days. The duration of the period of infection was 161 days. At the time of necropsy attempts were made to obtain cultures of tubercle bacilli from the spleens of the respective animals in the groups that were treated. Tissues were preserved for subsequent histopathologic studies.

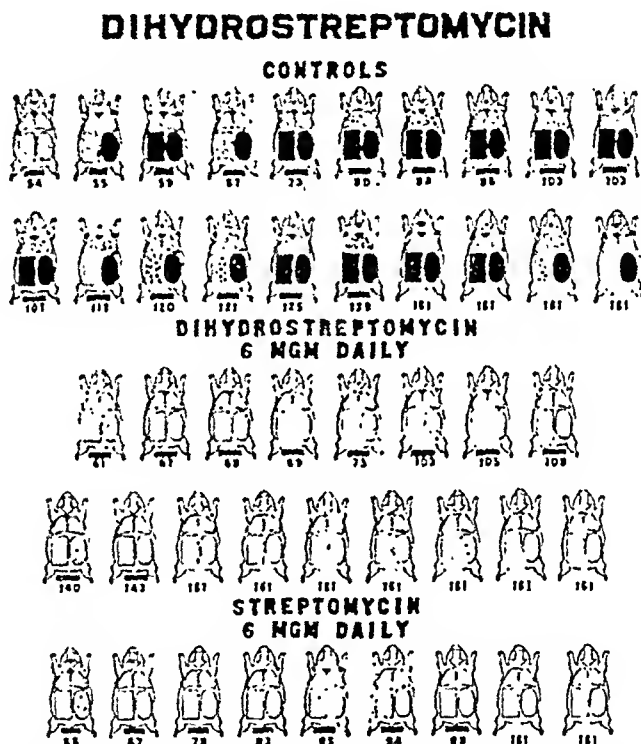


FIG. 1. Schematic representation of 46 guinea pigs each inoculated with 0.001 mg. of streptomycin-sensitive tubercle bacilli H37Rv. The two groups of animals that were treated had impressively less tuberculosis than did the untreated controls.

### Results

**Mortality rate:** Of the 20 animals in the control or untreated group, 16 (80 per cent) died. The first death occurred on the fifty-fourth postinfection day and the last death occurred on the one hundred and twenty-ninth postinfection day. A large number of deaths also occurred among the animals in the two

<sup>4</sup> The preparation supplied was stated by the manufacturer to be 95 per cent pure; hence, it was administered on an actual weight basis. Furthermore, the manufacturer's *in vitro* tests against *M. tuberculosis* H37Rv indicated that this preparation was comparable in potency to streptomycin.

<sup>5</sup> The streptomycin and the dihydrostreptomycin were kindly supplied through the courtesy of Merck & Co., Inc., Rahway, New Jersey.

groups that were treated. Ten (59 per cent) of the 17 animals that received dihydrostreptomycin died in the period from the sixty-first through the one hundred and forty-third postinfection day. Among the 9 animals in the group treated with streptomycin, 7 died in the period from the sixty-sixth through the ninety-eighth postinfection day.

Tuberculosis was the probable cause of death of each of the animals in the untreated group. At least, the character and extent of tuberculosis in this group were sufficiently severe to justify this conclusion (figure 1).

In contrast, among the two groups of animals that were treated, the amount of tuberculosis, gross and microscopic, was insufficient to account for death. The results of subsequent studies indicated definitely that, among the animals in these two groups that died prematurely, lymphocytic choriomeningitis was the most likely cause of death. The virus of this disease was demonstrated in the tissues of each animal in the treated groups that died, and was also obtained from other guinea pigs maintained in the same quarters as those in which the animals in this experiment were housed<sup>6</sup>.

TABLE 1

*Comparison of severity of tuberculosis determined microscopically in untreated controls and in groups treated with dihydrostreptomycin and with streptomycin*

| GROUPS OF GUINEA PIGS              | ANIMALS | SPLEEN<br>(MAX. 35) | LUNGS<br>(MAX. 30) | LIVER<br>(MAX. 25) | SITE OF<br>INOCU-<br>LATION<br>(MAX. 10) | AVERAGE<br>INDEX OF<br>INFECTIONS<br>(MAX. 100) |
|------------------------------------|---------|---------------------|--------------------|--------------------|--|---|
| Controls.....                      | 20      | 35.0                | 21.5               | 22.0               | 9.5                                      | 88.0  |
| Treated with dihydrostreptomycin.. | 17      | 0.8                 | 2.5                | 0.4                | 0.9                                      | 4.6   |
| Treated with streptomycin.....     | 9       | 1.2                 | 1.5                | 0.6                | 3.4                                      | 6.7   |

Fortunately, the viral infections did not become manifest until after the animals in group 2 and group 3 had been on treatment for approximately three weeks and, as a consequence, effects of antituberculosis treatment were evident even though many of the animals died prematurely. There was no evidence that treatment had any effect on the viral infection.

*Evidence of therapy:* As may be noted in figure 1, there was a striking dissimilarity in the amount of tuberculosis present in the untreated controls and in those animals treated with dihydrostreptomycin or with streptomycin. The antituberculosis potency of each of these agents was impressively demonstrated. This capacity of both dihydrostreptomycin and streptomycin was clearly apparent not only from the gross findings at necropsy, but also by microscopic examination of the tissues obtained from the animals in the respective groups.

In table 1, the comparative amounts of tuberculosis in the organs of predilection, expressed numerically as the average index of infection, are shown<sup>7</sup>.

<sup>6</sup> The demonstration and identification of the virus of lymphocytic choriomeningitis were accomplished by our associates, Dr. F. R. Heilman and Dr. Lyle W. Weed, of the Section on Bacteriology.

<sup>7</sup> The scheme used for recording, numerically, tuberculous changes in experimentally infected animals has been described previously (6).

That the average index of infection for the animals in the untreated group was 88 on the basis of a theoretical maximum of 100 indicates the potential pathogenicity of the infective agent. Furthermore, it should be recalled that the infection in the two groups of animals that were treated had been present for forty-two days before treatment was started. Several animals that died, prior to the forty-second day, showed at necropsy severe and widely disseminated tuberculosis. This provides reasons for believing that, in the animals that were treated, the disease was firmly established in the liver, spleen and lungs at the time when treatment was started.

The evidence suggests that the deterrent action of the respective therapeutic agents was exerted promptly and effectively. It is reasonable to assume that, had the viral infection not caused the premature death of animals in the groups that were treated, the results of treatment would have been even more impressive. This is especially true in the tuberculous involvement of certain lymph nodes. Many of these showed some active tuberculosis microscopically even though the disease in the parenchymal organs had undergone marked regression characterized by fibrotic changes and calcification.

*Bacteriologic cultures:* The results of the attempts to recover tubercle bacilli by cultural procedures from the spleens of the treated animals indicate the failure of both streptomycin and dihydrostreptomycin to exert a complete sterilizing effect. While it is true that negative cultures were obtained from many of the spleens, the positive cultures obtained indicate that the capacity of dihydrostreptomycin to kill tubercle bacilli in infected tissues is limited. This is also true of streptomycin (7).

The data obtained on the therapeutic efficacy of dihydrostreptomycin in experimental tuberculosis suggest that, under the conditions imposed in the experiment described, this derivative of streptomycin is a highly effective antagonist of tuberculosis. Therapeutically, there is insufficient evidence to warrant the belief that, in experimental tuberculosis, dihydrostreptomycin is more effective than is streptomycin. It may be assumed, however, that the antituberculosis potentials of these two substances are approximately equal.

## EXPERIMENT 2

The objective of this experiment was to determine the efficacy of dihydrostreptomycin against streptomycin-resistant tuberculous infections.

### *Methods*

Two groups of guinea pigs were used. Each animal received subcutaneously 0.1 mg. of human type of tubercle bacilli, resistant *in vitro* to more than 1,000 micrograms of streptomycin per milliliter<sup>3</sup>. Beginning twenty-one days after inoculation, one group consisting of 8 animals was treated with dihydrostreptomycin. Each animal received 6 mg. of the drug subcutaneously daily. The 10 animals in the second group served as the untreated controls. The experiment was terminated on the one hundred and thirtieth postinfection day. The 4 animals surviving in the group that received dihydrostreptomycin had been treated for 109 days at the time of necropsy.

<sup>3</sup> The culture was isolated from a patient who had received streptomycin for several months.



### Results

The results of experiment 2 showed clearly that dihydrostreptomycin had failed to exert any recognizable influence on the course of an infection induced by tubercle bacilli resistant to streptomycin. All animals that received treatment had widely disseminated, severe tuberculosis, comparable to the disease in the untreated controls (figure 2). It appears, therefore, that tubercle bacilli that are therapeutically resistant to streptomycin are similarly resistant to dihydrostreptomycin.

## DIHYDROSTREPTOMYCIN

### STREPTOMYCIN RESISTANT INFECTION

#### CONTROLS



### DIHYDROSTREPTOMYCIN

#### 6 MCGM DAILY



FIG. 2. Schematic representation showing the amount of tuberculosis at necropsy in 18 guinea pigs each infected with 0.1 mg. of human strain tubercle bacilli resistant to more than 1,000 micrograms of streptomycin per milliliter. The failure of dihydrostreptomycin to exert an effective therapeutic action is apparent. The second, third and fourth of the controls were killed for examination on the twenty-first day after infection.

### *In Vitro* Observations

The *in vitro* activity of dihydrostreptomycin was found to be the same as that of streptomycin when tested against 24 cultures of tubercle bacilli in egg yolk agar. The tests were done in parallel in tubes of egg yolk agar (8) containing 1, 10, 50, 100 and 1,000 micrograms of the respective compounds per milliliter of medium. Control tubes of medium not containing any antibiotic substance were included for comparison<sup>\*</sup>. Equal portions of a suspension of the culture being tested were inoculated on each slant of medium. After fourteen days of incubation, the resistance of the culture to dihydrostreptomycin and to streptomycin was recorded as the maximal concentration of the respective compound in micrograms per milliliter of medium which permitted growth comparable to that in the control tube.

Seven cultures that were found to be resistant to more than 1,000 micrograms of streptomycin per milliliter of medium were also resistant to more than 1,000 micrograms of dihydrostreptomycin per milliliter. Another culture was resistant to 50 micrograms of streptomycin per milliliter although it produced a few

\* The procedure followed in making the *in vitro* assays is that described by Karlson and Needham (8).

colonies on the tube containing 100 micrograms of streptomycin per milliliter. This culture was resistant to 100 micrograms of dihydrostreptomycin per milliliter. This difference is within the limits of error in a multiple dilution method.

The other 16 cultures were resistant to only 1.0 or less than 1.0 microgram of streptomycin per milliliter of medium and were also resistant to only 1.0 or less than 1.0 microgram of dihydrostreptomycin per milliliter.

Edison and her co-workers (3) also stated that dihydrostreptomycin and streptomycin are closely comparable in activity on a weight for weight basis against tubercle bacilli when tested *in vitro* against cultures of *Mycobacterium tuberculosis* (H37Rv).

#### COMMENT

Any new drug which is proposed for the treatment of clinical tuberculosis should be subjected to adequate study by means of well-controlled animal experimentation. It is desirable to demonstrate that the disease process may be suppressed under difficult circumstances and that the effect is not merely prophylactic, but is actually effective therapeutically against a well-established and widely disseminated tuberculosis infection. Furthermore, it is believed that new drugs should be tested in comparison with drugs of established tuberculotherapeutic merit, such as streptomycin and promin. These basic principles have been adhered to in investigating this latest antituberculosis drug, dihydrostreptomycin.

#### SUMMARY

A study was done to determine the antituberculosis efficacy of dihydrostreptomycin. A group of guinea pigs was inoculated subcutaneously, each animal receiving 0.001 mg. of streptomycin-sensitive human strain tubercle bacilli, H37Rv. Beginning forty-two days later, one group of 17 animals was treated with 6.0 mg. of dihydrostreptomycin daily and one group of 9 animals received 6.0 mg. of streptomycin subcutaneously daily. The remaining 20 animals served as controls. The experiment continued for a total of 161 days after the animals had received the infective dose of tubercle bacilli. The period of treatment was 119 days. The results of this phase of the study indicated definitely that the antituberculosis potency of dihydrostreptomycin was equal to that of streptomycin.

In another study the effectiveness of dihydrostreptomycin against experimental tuberculosis induced by a human strain of tubercle bacilli resistant to more than 1,000 micrograms of streptomycin per milliliter of medium was determined. In this study dihydrostreptomycin failed to produce any recognizable therapeutic effect.

#### CONCLUSIONS

(1) In experimental tuberculosis due to streptomycin-sensitive tubercle bacilli of the human type, dihydrostreptomycin, on a comparable weight basis, is equally effective therapeutically as its parent substance, streptomycin.

(2) Dihydrostreptomycin has little, if any, potential value therapeutically in experimental infections induced by so-called streptomycin-resistant tubercle bacilli.

## SUMARIO

*Dihidroestreptomycin: Su Efecto sobre la Tuberculosis Experimental*

Este estudio tuvo por objeto determinar la eficacia antibacteriana de la dihidroestreptomycin. Un grupo de 46 cobayos fué inoculado subcutáneamente, recibiendo cada animal 0.001 mg. de una cepa de bacilos tuberculosos humanos, estreptomycinosensibles, H37Rv. Comenzando 42 días después, un grupo de 17 animales fué tratado con 6 mg. diarios de dihidroestreptomycin y otro grupo de 9 animales con 6 mg. diarios de estreptomycin por vía subcutánea. Los otros 20 animales sirvieron de testigos. El experimento continuó hasta un total de 161 días a partir de la fecha en que los animales recibieron la dosis infectiva de bacilos tuberculosos. El tratamiento duró 119 días. Los resultados de esta fase del estudio indicaron netamente que la potencia anti-tuberculosa de la dihidroestreptomycin es igual a la de la estreptomycin.

En otro estudio se determinó la eficacia de la dihidroestreptomycin contra la tuberculosis experimental inducida por una cepa humana de bacilos tuberculosos resistentes a más de 1,000 microgramos de estreptomycin por mililitro de medio. En este estudio la dihidroestreptomycin no produjo ningún efecto terapéutico discernible.

## CONCLUSIONES

(1) En la tuberculosis experimental debida a bacilos tuberculosos estreptomycinosensibles de tipo humano, la dihidroestreptomycin, a base comparable por peso, iguala en eficacia terapéutica la sustancia madre: la estreptomycin.

(2) La dihidroestreptomycin posee poco, o ningún, valor terapéutico potencial en las infecciones experimentales evocadas por los bacilos tuberculosos llamados estreptomycinorresistentes.

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# A LABORATORY AND CLINICAL INVESTIGATION OF DIHYDROSTREPTOMYCIN<sup>1, 2, 3</sup>

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## INTRODUCTION

Dihydrostreptomycin is an antibacterial agent which has been prepared by catalytic hydrogenation of streptomycin. It differs from the latter structurally only in having a hydroxyl instead of a carbonyl group in the streptobiosamine portion of the molecule (1, 2, 3). The dihydro derivative has been reported to be slightly less toxic than streptomycin as measured by the LD<sub>50</sub> in mice (4), and the two compounds are active against the same micro-organisms *in vitro* (2, 4). There are quantitative differences in the antibacterial effectiveness of the two compounds, the dihydro derivative being slightly less active against most strains (2, 4, 5). Donovan and Rake observed that streptomycin-resistant strains of *H. influenzae* were also resistant to dihydrostreptomycin, and this finding has been confirmed on resistant strains of other species in this laboratory. These early reports did not suggest any advantage of dihydrostreptomycin over the parent compound for clinical use, unless the derivative were significantly different in its distribution or toxicity.

Certain of the toxic reactions observed during the administration of streptomycin to humans were not previously disclosed by routine toxicity tests in animals. Examples of these include several manifestations of hypersensitivity such as fever, skin eruptions, asthma, and eosinophilia, which may be encountered during prolonged streptomycin treatment. Occasionally, these hypersensitivity reactions have been so severe that therapy had to be abandoned or interrupted for many weeks. An even more severe limitation on the usefulness of streptomycin results from its neurotoxicity, notably the involvement of vestibular and auditory functions.

It is generally recognized that slight changes in chemical composition may alter the capacity of a drug to give rise to manifestations of hypersensitivity. Dihydrostreptomycin, with a greatly altered polar group, might be expected to differ significantly from streptomycin in this regard. It is also recognized that

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other manifestations of toxicity may be altered by such slight chemical changes. A striking example of such alteration has been reported by Schmidt (6), who found that the introduction of a single hydroxyl group into the side chain of 6-methoxy derivatives of 8-aminoquinolines reduced their specific neurotoxicity by 75 per cent.

It seemed possible, therefore, that dihydrostreptomycin might be different from streptomycin in its toxicity for humans despite the similarity of the two drugs in other respects. Accordingly, in March 1947 a laboratory and clinical investigation of dihydrostreptomycin was started and the results observed form the basis for the present report. The greater portion of the study was planned to determine: (1) if dihydrostreptomycin were toxic; (2) how its toxicity compared with that of streptomycin; and (3) what its relative therapeutic effectiveness might be. In investigating the first two of these points, both clinical and animal studies were made. Cats were chosen, since this animal had been used previously for investigations of the neurotoxicity of streptomycin (7, 8, 9).

## OBSERVATIONS

### MATERIALS AND METHODS

**Drug:** Two preparations of dihydrostreptomycin were used in this study: (1) A "crude" preparation assaying 342 to 573 units per mg. (0.34 to 0.57 grams of "active base" per gram of solid material). This was made by the catalytic hydrogenation of crude streptomycin complex, a mixture of streptomycin and mannosidostreptomycin (10), previously termed streptomycin A and B. It was received as a powder, made up as a solution containing 1.0 Gm. of "base" in each 4 cc. of distilled water, and sterilized by filtration. (2) A "purified" material prepared from highly purified streptomycin hydrochloride and assaying about 750 units per mg. (0.75 grams of "base" per gram of solid). This was supplied in vials as a sterile white powder, each vial containing 1.0 Gm. of "base" which was taken up in 4 cc. of sterile distilled water before use. Each lot of dihydrostreptomycin had been found free of pyrogens and histamine-like substances.

The potency of dihydrostreptomycin was determined by assay against streptomycin standards using *Klebsiella pneumoniae* as the test organism. The strain used had been shown to be equally sensitive to the two compounds (4), so that one "unit" of dihydrostreptomycin thus determined was equivalent to one "unit" of streptomycin. Throughout this paper, the accepted convention of considering one unit of streptomycin as equal to one microgram has been extended to dihydrostreptomycin. All references to amounts of dihydrostreptomycin are given in metric weights of the "active base" rather than units so that 5.0 Gm. of dihydrostreptomycin can be read as 5,000,000 units of the antibacterial agent rather than as 5.0 Gm. of total solid.

It was found that passage through a Seitz filter did not alter the antibacterial potency of the solutions of either the dihydrostreptomycin or streptomycin which were used.

**Bioassays:** Assays for dihydrostreptomycin were made by a modification of the method of Stebbins and Robinson (11) using paper discs. *Staphylococcus aureus* ("Staph SM" strain) was the test organism and dihydrostreptomycin standards were used for fluids containing that drug. The use of the corresponding drug in the standard is important for, unless the test strain is known to be equally sensitive to dihydrostreptomycin and streptomycin, considerable error may be introduced by using a streptomycin standard in the determination of dihydrostreptomycin.

*Tests of vestibular function:* Vestibular function was tested by a modification of Kobrak's procedure (12), with the patient's head held at a 30 degree angle so that the anterior canal was stimulated. The water used was at 15 to 20° C. and, if a response was obtained, only one ear was tested. Although the time of onset and the duration of nystagmus were both noted, it was arbitrarily decided to consider the response abnormal if more than 90 seconds' irrigation was required to produce nystagmus. If no nystagmus occurred after three minutes' irrigation, the response was considered "absent."

Each patient had stereoscopic roentgenograms of the chest at two week intervals, frequent urinalyses, and determinations of the peripheral blood cell count, erythrocyte sedimentation rate, and the blood urea nitrogen. Urea clearance tests were obtained in the later cases.

#### ABSORPTION, EXCRETION AND DISTRIBUTION OF DIHYDROSTREPTOMYCIN

Donovick and Rake (4, 5) found that the excretion of dihydrostreptomycin is similar to that of streptomycin in mice. Any difference in the toxicity of the two compounds might be due to different rates of absorption and excretion, however, or to the failure of one compound to reach the susceptible tissue to the same degree. Therefore, the concentration of dihydrostreptomycin in the serum of cats and in the serum and cerebrospinal fluid of humans was studied after intramuscular administration of the compound.

Two cats, which had already received sixteen daily injections of "crude" dihydrostreptomycin, 200 mg. per kg., were given that intramuscular dose again. Blood was drawn at intervals over the next twenty-four hours for assay of the serum concentration of the drug. The 2 cats which had been similarly treated with streptomycin served as controls.

Four patients were each given 20 mg. per kg. of "crude" dihydrostreptomycin intramuscularly, and one patient was given 23.6 mg. per kg. of the "purified" preparation. The serum concentrations of the drug were then determined at intervals over the next four hours. The cerebrospinal fluid content was measured on a single specimen from each of 2 patients, neither of whom had any evidence of meningitis. Both patients had received "crude" dihydrostreptomycin, 1.0 Gm., five times daily for a period of five days. The last injection was given fourteen hours prior to lumbar puncture.

In figure 1 may be seen the serum concentrations of the two compounds in the 4 cats. The upper two curves represent the values in the 2 animals which received dihydrostreptomycin. The lower curve represents the average values in 2 cats given streptomycin.

In figure 2 are presented the results of serum assays in the humans. Curve A is a composite for all 4 patients who received 20 mg. per kg. of dihydrostreptomycin. Curve C is drawn through points representing the average concentrations of streptomycin in 4 patients who had been given 20 mg. per kg. of that compound.

The two samples of cerebrospinal fluid contained respectively 8.1 and 7.5 micrograms per cc. of dihydrostreptomycin.

The serum concentration of dihydrostreptomycin one hour after intramuscular administration and the rate of fall in concentration thereafter are comparable to

values obtained with streptomycin in both man and cat. Although the rate of fall may be slightly slower than that of streptomycin in man (see curve C and also 13, 14, 15, 16), this is not verifiable statistically from these data. It seems that the two compounds have approximately the same rate of absorption and excretion, so that these factors would not explain any difference in toxicity.

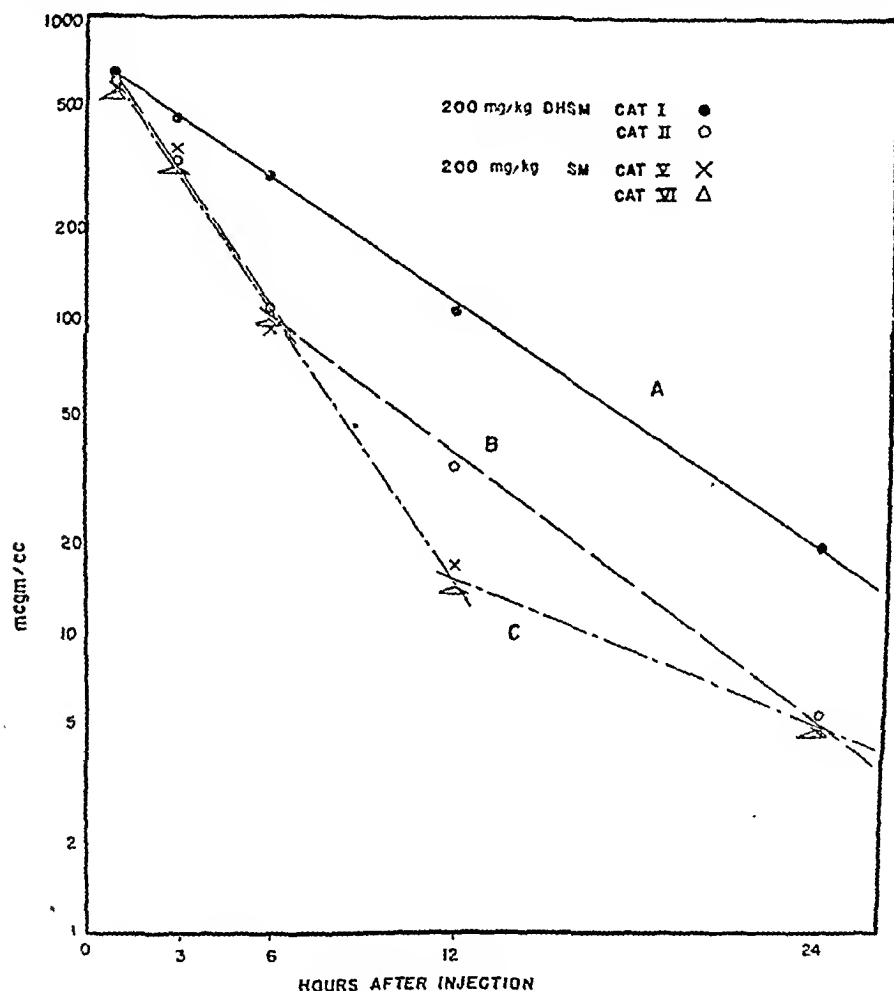


FIG. 1. Serum concentrations of dihydrostreptomycin (DHSM) and streptomycin (SM) in cats following intramuscular injection of a single large dose (200 mg./kg.). Curves A and B represent the values obtained in the two animals given dihydrostreptomycin. Curve C is drawn from the averages of determinations in the two animals given streptomycin.

Streptomycin penetrates the intact central nervous system to a limited degree and may attain concentrations in the neighborhood of 5.0 micrograms per cc. in the cerebrospinal fluid (13, 14, 17, 18). In the patients reported here, the concentrations of dihydrostreptomycin in the cerebrospinal fluid (8.1 and 7.5 micrograms per cc.) were not significantly different from these values for streptomycin. Thus it is unlikely that differences in the neurotoxicity of the two drugs

could be explained on the basis of failure of either to penetrate the blood-brain barrier.

#### NEUROTOXICITY OF DIHYDROSTREPTOMYCIN

In the studies of the neurotoxicity of dihydrostreptomycin, treatment regimens were purposely chosen which, on a unitage basis, would be well within the toxic range of streptomycin.

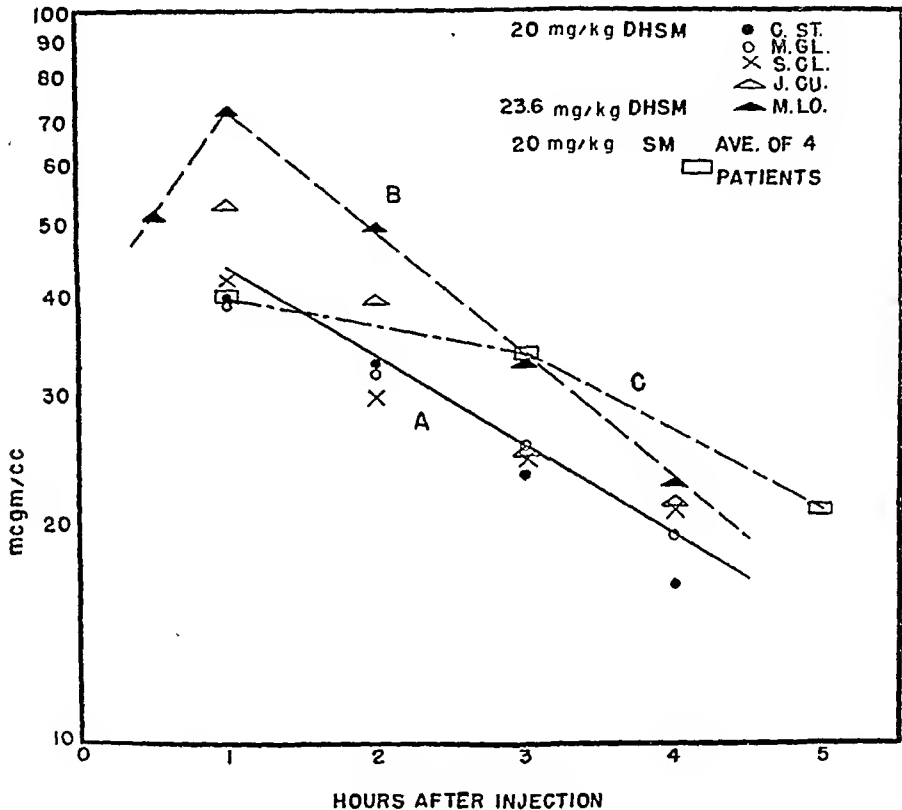


FIG. 2. Serum concentrations of dihydrostreptomycin (DHSM) and streptomycin (SM) in man following intramuscular administration of single doses. Curves A and C each represent averages of values obtained in four patients given 20 mg./kg. of dihydrostreptomycin and streptomycin, respectively. Curve B is drawn through values obtained in one patient who received 23.6 mg./kg. of dihydrostreptomycin.

#### Cats

Six cats were given large intramuscular doses of either "crude" dihydrostreptomycin (474 units per mg.) or purified streptomycin (727 units per mg.). Each animal was weighed weekly and the dose was determined by the most recent weight. Two cats received 200 and 400 mg. per kg. per day of dihydrostreptomycin in one injection daily. Two control cats were given 200 mg. per kg. per day of streptomycin.

Each animal was examined just prior to the daily injection for signs of awkwardness, spontaneous nystagmus, general state and behavior. Any detectable difficulty in using the legs or in maintaining balance was considered "awkwardness." Marked impairment



of balance and coordination so that the animal was unable to stand quietly upright on a level surface was designated "gross ataxia." Tipping and tossing the animal were used to detect awkwardness, but rotational tests were not employed, as awkwardness appears at the same time that this test first detects vestibular dysfunction (9).

After the appearance of gross ataxia, the injections were continued. The dose was progressively increased in the cats receiving 200 mg. per kg. per day initially until all the animals died of toxicity. The brains and viscera were examined grossly and microscopically and the findings will be presented in detail elsewhere.

In table 1 may be seen the effects of massive doses of dihydrostreptomycin and streptomycin on the coordination and balance of the cats. Dihydrostreptomycin produced vestibular damage in the dosages used, but the effects were apparent earlier in the controls treated with streptomycin. Spontaneous nystagmus was never observed in any of the animals.

TABLE 1  
*Neurotoxicity of streptomycin and dihydrostreptomycin in cats*

| DRUG                | DOSE                     | CAT | DAY OF ONSET OF |              | WEIGHT           |                           | DAY OF DEATH |
|---------------------|--------------------------|-----|-----------------|--------------|------------------|---------------------------|--------------|
|                     |                          |     | Awkwardness     | Gross Ataxia | Before injection | After 17 daily injections |              |
| Dihydrostreptomycin | 200<br><i>mg./kg./d.</i> | I   | 17-18           | 19           | 2.17             | 1.87                      | —            |
|                     |                          | II  | 15              | 18           | 4.42             | 2.58                      | —            |
| Streptomycin        | 200                      | V   | 11              | 13           | 2.92             | 2.08                      | —            |
|                     |                          | VI  | 8               | 13           | 2.26             | 1.82                      | —            |
| Dihydrostreptomycin | 400                      | III | 3               | 8            | 3.05             | —                         | 19           |
|                     |                          | IV  | 3               | ?            | 3.53             | —                         | 8            |

All 6 cats had excessive salivation and anorexia. This appeared after the first injection of 400 mg. per kg. of dihydrostreptomycin, and within the first week all 4 cats on the smaller dose of either compound also showed the same signs although to a lesser degree. Considerable debilitation resulted, as may be seen by the weight loss recorded in table 1, but the loss of balance and coordination did not exactly parallel the degree of debility.

Hawkins and O'Shanny (9) have found that cats injected with 100 mg. per kg. per day of streptomycin hydrochloride became awkward after thirteen to twenty-four days. Thirty-two to fifty-one days were required to reach the same end point when the same dose of the calcium chloride complex was given. As larger doses of streptomycin produce vestibular dysfunction more quickly, the production of awkwardness on the eighth and eleventh days with 200 mg. per kg. per day of streptomycin is in accord with the results of Hawkins and O'Shanny. They found such wide variations in the time of onset of awkwardness, however, that the later appearance of vestibular dysfunction in cats given 200 mg. per kg. per day of dihydrostreptomycin may not be significant.

In this small series of cats evidence was obtained which indicated that dihydrostreptomycin produces essentially the same neurotoxic signs as streptomycin, and that possibly these manifestations appeared later when the dihydro derivative was used. It was felt that the latter possibility could be investigated more satisfactorily in humans, and animal experiments were abandoned in favor of clinical trials.

### *Humans*

Ten patients were treated with large doses of dihydrostreptomycin, and an additional 2 received smaller doses for long periods of time. The significant data concerning each of these patients are presented in tables 2, 3, and 4. These 12 patients were men and women from 15 to 60 years of age. All had moderately or far advanced, active, pulmonary tuberculosis; 6 (Cases 1, 2, 4, 6, 9, 10) were known to have had a spread of the pulmonary disease less than two months before treatment was begun. In addition to their lung lesions, 2 patients had demonstrable acute lymphohematogenous dissemination without meningitis (Cases 3, 5). Tubercle bacilli were cultured from the urine of 2 others (Cases 2, 4). There were also 2 patients with tuberculous ulceration of the upper respiratory tract (Cases 11, 12) and one with tuberculous otitis media (Case 7). Alcoholism and hepatic cirrhosis (Cases 2, 5) and diabetes with hypertension (Case 6) were nontuberculous complications.

Two patients (Cases 1 and 7) had received streptomycin intramuscularly before dihydrostreptomycin was begun, and Case 11 had had topical applications of streptomycin to an oral ulcer for six months prior to admission. One patient (Case 1) also had a course of para-aminosalicylic acid just before dihydrostreptomycin was started. In two instances (Cases 3, 11), streptomycin was begun two days after the available supply of dihydrostreptomycin was exhausted.

The first 9 patients in the series received "crude" dihydrostreptomycin and in 6 the impure material was used exclusively. As the content of active base is low in this preparation (see above), some patients received as much as 14 Gm. per day of total solids in a concentrated solution. Thus, in addition to the stated dose of active antimicrobial substance, the material administered presumably contained variable amounts of streptomycin-like compounds which had little or no antimicrobial activity. It is conceivable, however, that these compounds might add to the toxicity of the material injected. During the latter part of the study, "purified" dihydrostreptomycin was given to all patients. The dihydrostreptomycin therapy of each of the 12 cases may be seen in table 2. The intramuscular route was the only one used.

Six patients received 5.0 Gm. of dihydrostreptomycin daily (in divided doses of 1.0 Gm. each) for sixteen to seventy-eight days, 5 of them for more than thirty days. The total amount used per patient ranged from 74 to 365 Gm. Two patients were given the "crude" or "purified" preparation in doses of 3.0 Gm. daily for forty-two days, a total of 126 Gm. per patient. One patient received 3.0 Gm. daily of the "purified" preparation for thirty-three days, a total of 97 Gm., and 2 patients were treated with 1.0 Gm. of "purified" dihydrostreptomycin in a single daily injection for forty-six and twenty-five days respectively. The remaining patient was given the "crude" preparation, 5.0 Gm. daily for thirteen days, and then 3.0 Gm. of one or the other preparation daily over sixty-five days, a total of 232 Gm.

The dose of dihydrostreptomycin ranged from 18 to 110 mg. per kg. body weight per day (See table 2). It was occasionally necessary to reduce the daily

dose or to discontinue treatment for a few days when the injections of "crude" dihydrostreptomycin became too painful or when the supply was temporarily

TABLE 2  
*Specific therapy received by patients*

| CASE<br>NUM-<br>BER | PATIENT | DIHYDROSTREPTOMYCIN THERAPY |        |         |          |       | OTHER ANTIBACTERIAL THERAPY <sup>2</sup>  |
|---------------------|---------|-----------------------------|--------|---------|----------|-------|---|
|                     |         | Dura-<br>tion <sup>1</sup>  | Dosage |         |          |       |   |
|                     |         |                             | Daily  | Daily   | Per dose | Total |   |
|                     |         | days                        | Gm.    | mg./kg. | mg./kg.  | Gm.   |   |
| 1                   | G. Sc.  | 78                          | 5.0    | 90      | 18       | 365   | SM, 1.0 Gm. daily for 84 days, completed 58 days earlier. PAS, 15 Gm. daily for 66 days, completed on day DHSM was begun.             |
| 2                   | S. Cl.  | 73                          | 5.0    | 80      | 16       | 324   | None  |
| 3                   | W. Es.  | 37                          | 5.0    | 65      | 13       | 176   | SM, 1.0 Gm. daily for 56 days, begun 2 days later.  |
| 4                   | C. Ve.  | 45                          | 5.0    | 90      | 18       | 216   | None  |
| 5                   | A. Fl.  | 16                          | 5.0    | 110     | 23       | 74    | None  |
| 6                   | E. Ky.  | 32                          | 5.0    | 80      | 16       | 135   | None  |
| 7                   | S. Mo.  | 13                          | 5.0    | 75      | 15       | 61    | None (Still under treatment)  |
|                     |         | 26                          | 3.0    | 45      | 15       | 78    |   |
|                     |         | 59 <sup>3</sup>             | 3.0    | 45      | 15       | 93    |   |
|                     |         | 78                          |        |         |          | 232   |   |
|                     |         |                             |        |         |          |       |   |
| 8                   | J. Ni.  | 27                          | 3.0    | 50      | 16       | 81    | None  |
|                     |         | 15                          | 3.0    | 50      | 16       | 45    |   |
|                     |         | 42                          |        |         |          | 126   |   |
| 9                   | J. St.  | 15                          | 3.0    | 40      | 14       | 45    | None  |
|                     |         | 27                          | 3.0    |         |          | 81    |   |
|                     |         | 42                          |        |         |          | 126   |   |
| 10                  | D. Wi.  | 33                          | 3.0    | 50      | 17       | 97    | None  |
| 11                  | R. Pi.  | 46                          | 1.0    | 18      | 18       | 43    | Topical SM to tongue for 180 days in another institution completed 6 days earlier. SM, 1.0 Gm. daily for 47 days, begun 2 days later. |
| 12                  | M. Lo.  | 25                          | 1.0    | 23      | 23       | 22.4  | SM, 3.0 Gm. daily for 19 days, completed 35 days earlier.   |

<sup>1</sup> Duration generally includes some days on diminished dose and a few "rest periods."

<sup>2</sup> SM—streptomycin; PAS—para aminosalicylic acid; DHSM—dihydrostreptomycin.

<sup>3</sup> Numbers in italics refer to "purified" dihydrostreptomycin, others are "crude."

exhausted. Thus, the total amounts of drug received are not always the product of the daily dose and the number of days over which treatment was given. The data on the toxic manifestations of dihydrostreptomycin are presented in table<sup>3</sup>.

TABLE 3  
Toxic reactions to dihydrostreptomycin

| CASE NUMBER | PATIENT | DOSE        | VESTIBULAR (DAY OF ONSET)                              |                  |        | AUDITORY   |              |                                 | RENAL   |                           | FOLLOW-UP PERIOD SINCE START OF THERAPY |
|-------------|---------|-------------|--|------------------|--------|--|--------------|---------------------------------|---|---------------------------|---|
|             |         |             | "Dizziness"  | Caloric response |        | Symptom  | Day of onset | Audiometric loss (day of onset) | Manifestation   |                           |   |
|             |         |             |  | Abnormal*        | Absent |  |              |                                 |   |                           |   |
| 1           | G. Sc.  | 5.0         | (44), 72   | (35) (68)        | 78     | High pitched deafness and tinnitus                       | 60           | 157                             | None  | 7 months                  |   |
| 2           | S. Cl.  | 5.0         | (61)   | —                | 84     | Tinnitus   | 155          | None                            | None  | 6 months                  |   |
| 3           | W. Es.  | 5.0         | 42   | 41               | <152   | "Fullness in ears" <sup>†</sup><br>High pitched deafness | 30<br>44     | 137                             | Albuminuria<br>(had been present once before treatment) | 28<br>6 months            |   |
| 4           | C. Ye.  | 5.0         | None   | —                | 33     | Increasing deafness<br>Complete deafness                 | 42<br>48     | —                               | Albuminuria<br>Elevated BUN<br>Uremic death             | 26<br>39<br>54<br>54 days |   |
| 5           | A. Fl.  | 5.0         | None in 16 days  |                  |        | None in 16 days  |              | —                               | None  | 16 days                   |   |
| 6           | E. Ky.  | 5.0         | (29)   | Never            | Never  | None   |              | None                            | Elevated BUN  | 27<br>34 months           |   |
| 7           | S. Mo.  | 5.0 and 3.0 | No evident toxicity at 78 days (still under treatment) | Never            | Never  | None   |              | None                            | None  | 2 months                  |   |
| 8           | J. Ni.  | 3.0         | None   | Never            | Never  | None   |              | None                            | None  | 2 months                  |   |
| 9           | J. Sl.  | 3.0         | None   | Never            | Never  | None   |              | None                            | None  | 5 weeks                   |   |
| 10          | D. Wi.  | 3.0         | None   | —                | (32)   | None   |              | None                            | None  | 13 months                 |   |
| 11          | R. Pi.  | 1.0         | None   | —                |        | None   |              | None                            | None  | 19 months                 |   |
| 12          | M. Lo.  | 1.0         | 21†  | Never            | Never  | None   |              | None                            | None  |                           |   |

\* Onset delayed beyond 90 sec. by modified Kobrak test.

† Had been experienced before treatment.

Figures in parentheses indicate mild, transient episodes.

Figures in italics indicate toxicity after discontinuance of therapy but dated from start of treatment.

Four of the 5 patients who received 5.0 Gm. of dihydrostreptomycin over thirty days or longer had definite damage to both auditory and vestibular function. In every instance, the vestibular damage was apparent before the hearing was affected. Only one of the 4 patients treated with 3.0 Gm. of dihydrostreptomycin daily for thirty days or more had detectable loss of vestibular function.

*Vestibular dysfunction:* The earliest appearance of definite neurotoxicity was on the thirty-second and thirty-third days of treatment, when there was no response to caloric stimulation in two young women. It is of interest that neither of these patients ever experienced the "dizziness" characteristic of streptomycin toxicity (19). One of these women (Case 10) had received 3.0 Gm. of "purified" dihydrostreptomycin daily, had no evidence of renal damage and the vestibular dysfunction was only transient. The other (Case 4) had been given 5.0 Gm. of "crude" dihydrostreptomycin and later had evident renal damage, so that she may have been retaining the drug in unusually high concentrations before the thirty-third day, when the vestibular function was discovered to be abnormal. Another patient (Case 3) had an abnormal response to the caloric test on the forty-first day, and the onset of moderately severe, characteristic "dizziness" on the forty-second day. The administration of dihydrostreptomycin had been stopped on the thirty-seventh day, and streptomycin 1.0 Gm. daily had been started on the thirty-ninth day. His last normal caloric test was on the thirty-second day. The response to caloric testing became completely absent between the one hundred and second and one hundred and fifty-second days, approximately two months after dihydrostreptomycin was discontinued.

The first patient treated with large doses (Case 1) experienced transient but characteristic symptoms of vestibular dysfunction on the forty-fourth day. On the seventy-second day of treatment, these recurred and persisted for several days. Response to caloric stimulation was transiently abnormal on the thirty-fifth and sixty-eighth days, and became completely and permanently absent on the seventy-eighth day. One patient (Case 2) had a brief episode of "fuzzy vision" on the sixty-first day, and gave no response to caloric stimulation on the eighty-fourth day. The caloric response had been normal on the seventy-fifth day, two days after treatment was stopped. On the one hundred and sixty-eighth day after treatment was begun, and three months after the last dose, he had the onset of blurred vision for distant objects which has persisted to date, without any other symptoms of vestibular dysfunction.

The remaining patient (Case 6) had transient blurring of distant objects on the twenty-ninth day. Treatment was stopped three days later, and he never had any further symptoms or abnormal responses to caloric stimulation. One patient (Case 11) received 1.0 Gm. of "purified" dihydrostreptomycin daily over forty-six days followed by 1.0 Gm. of streptomycin daily for forty-seven days. She never experienced symptoms of vestibular dysfunction, but she gave no response to caloric stimulation on the one hundred and eighteenth day, two and a half months after dihydrostreptomycin was stopped and three weeks after the last streptomycin. Her caloric response had returned to normal on retesting 345 days after treatment was begun, ten months after it had been discontinued.

TABLE 4  
Types of disease and results of dihydrostreptomycin therapy

| CASE NO.<br>SER. | PATIENT | AGE<br>years | SEX | DIAGNOSES  |  | THERAPEUTIC RESULTS  |                                     |  |
|------------------|---------|--------------|-----|--|--|----------------------|-------------------------------------|--|
|                  |         |              |     | Pulmonary tuberculosis   | Others   | Röntgenogram         | Reversal of infectiousness (sputum) | General clinical improvement                                 |
| 1                | G. Se.  | 27           | F   | Very extensive, bilateral, cavitary, III D                                     | None   | Slight improvement   | No                                  | Slight   |
| 2                | S. Cl.  | 49           | M   | Extensive, bilateral, old and new lesions, III D; recent hemoptyses (figure 6) | Alcoholism, moderate cirrhosis                     | Moderate improvement | No                                  | Good   |
| 3                | W. Es.  | 42           | M   | Bilat. apical lesions, II B  | Miliary tuberculosis, recent                       | Marked improvement   | Apparently completely—18 days       | Excellent  |
| 4                | C. Ve.  | 16           | F   | Bilat. cavitary, III C, recent spread  | None   | Marked improvement   | Complete—27+ days                   | Good; death from toxicity                                    |
| 5                | A. Fl.  | 60           | F   | Bilat. extensive, cavitary, III D  | Miliary tuberculosis, alcoholism, marked cirrhosis | —                    | No                                  | Questionable; temperature fell, but patient died on 16th day |
| 6                | E. Ky.  | 55           | M   | Bilat. cavitary II C, recent spread  | Diabetes mellitus, hypertension                    | Slight improvement   | Complete—12 days                    | Slight   |
| 7                | S. Mo.  | 24           | F   | Very extensive, bilateral, cavitary, III D                                     | Tuberculosis otitis media                          | Moderate improvement | Cultures not completed              | Good   |
| 8                | J. Ni.  | 48           | M   | Bilat., extensive, cavitary, III D   | None   | Slight improvement   |                                     | Good   |
| 9                | J. St.  | 31           | M   | Unilat., II C, recent confluent spread (figure 7)                              | None   | Marked improvement   | Cultures not completed              | Good   |
| 10               | D. Wi.  | 15           | F   | Unilat., parahilar, with recent spread, II C                                   | None   | Marked improvement   |                                     | Good   |
| 11               | H. Pl.  | 36           | F   | Recent, extensive, bilateral, bronchogenic spread, III C (figure 8)            | Tuberculous ulcers of mouth and larynx             | Marked improvement   | Complete—35 days                    | Excellent  |
| 12               | M. Lo.  | 40           | F   | Very extensive bilateral, active, III D  | Laryngeal, pharyngeal tuberculosis                 | Marked improvement   | Transient—35 days                   | Good   |

Quantitative tests for the degree of disability from the loss of vestibular function were not attempted. It appeared, however, that patients in this series were less incapacitated than those who had received 3.0 Gm. of streptomycin daily for ninety days.

*Impairment of auditory function:* The first appearance of auditory difficulty was on the forty-second day of treatment, when deafness was first noticed by the patient (Case 4—5.0 Gm.) who had urea retention at that time. The deafness became complete on the forty-eighth day. Another patient (Case 3—5.0 Gm.) complained of "fullness and popping" in both ears on the thirtieth day. His ear drums were retracted at that time, and it was noted in his history that he had had similar episodes for many years. He experienced tinnitus and was unable to hear a watch tick after the forty-fourth day, by which time he had received no dihydrostreptomycin for eight days and had had streptomycin for six days. Frequent audiograms first showed hearing loss (13 per cent) on the one hundred and thirty-seventh day, three and a half months after he was last given dihydrostreptomycin.

Patient G. Sc. (Case 1—5.0 Gm.) began to have high-pitched tinnitus and became unable to hear a watch on the sixty-ninth day. Her deafness slowly increased, and audiograms first showed a hearing defect (15 per cent) on the one hundred and fifty-seventh day, almost three months after conclusion of her treatment. Another patient (Case 2—5.0 Gm.) first noted persistent tinnitus on the one hundred and fifty-fifth day, almost three months after treatment, but no audiograms are available after the ninety-second day from the start of therapy. None of these patients has had sufficient deafness to make conversation difficult.

#### USE OF DIHYDROSTREPTOMYCIN IN PATIENTS HYPERSENSITIVE TO STREPTOMYCIN

Five patients who had developed classical manifestations of hypersensitivity while receiving streptomycin intramuscularly were given "purified" dihydrostreptomycin in various doses by the same route. Small doses of different highly purified streptomycin salts were used to reproduce the hypersensitivity reactions. The usual clinical observations were made throughout the course of treatment with both drugs.

In table 5 the treatment given and the results obtained in each of 5 cases are summarized. In every patient the manifestations of hypersensitivity to streptomycin were reproduced by one or more injections of that drug after the symptoms had subsided. A single injection of 0.1 Gm. of streptomycin provoked an indisputable reaction each time it was given, but every patient was able to take dihydrostreptomycin without untoward effects within two days of the last streptomycin reaction. In figures 3, 4, and 5 may be seen examples of the clinical course of 3 of these patients who were hypersensitive to streptomycin.

It should be mentioned that the state of "hypersensitivity" to a drug does not always persist indefinitely. Many individuals are able to tolerate a drug only a few weeks or months after it has given rise to definite manifestations of "hypersensitivity." In the present series, however, the temporal relationships of the response of the patients to the individual drugs were so striking that it is con-

TABLE 5  
Effects of dihydrostreptomycin in patients hypersensitive to streptomycin

| CASE   | DIAGNOSIS  | DOSE STREPTOMYCIN   | SENSITIVITY REACTION           |  |  | DOSE DIHYDROSTREPTOMYCIN                        | SENSITIVITY REACTION TO DIHYDRO | THERAPEUTIC RESULTS |
|--------|--|---|--------------------------------|--|--|---|---------------------------------|---------------------|
|        |  |   | Day of onset                   | Symptoms, etc.   |  |   |                                 |                     |
| R. Sm. | Subacute bacterial endocarditis due to <i>S. fecalis</i> | 2.0 Gm. intramuscularly for 12 days   | 7th<br>12th                    | Increasing fever<br>Generalized maculopapular dermatitis       |  | 0.1 to 2.0 Gm. for 4 days                       | None                            |                     |
| Gia.   | Tuberculous lymphadenitis                                | 1.0 Gm. intramuscularly for 7 days  | 3rd                            | Increasing fever, malaise, vomiting                            |  | 0.1 to 0.4 Gm. for 2 days                       | None                            |                     |
| Sal.   | Leprosy  | 1.0 Gm. intramuscularly for 14 days   | 13th                           | Fever  |  | 0.1 Gm. for 29 days                             | None                            | No improvement      |
| R. Pl. | Tuberculosis of lungs, larynx and tongue                 | Daily topical application to tongue for 6 months then 1.0 Gm. intramuscularly for 1 day | First day of I.M. streptomycin | Chill, fever, malaise, urticaria                               |  | 0.01 to 0.7 Gm. for 3 days; 1.0 Gm. for 46 days | None                            | Marked improvement  |
| M. Jo. | Tuberculosis of lungs and larynx                         | 3.0 Gm. intramuscularly for 21 days   | 20th                           | Initial attack of asthma, generalized dermatitis, eosinophilia |  | 0.1 to 0.4 Gm. for 2 days; 1.0 Gm. for 21 days  | None                            | Marked improvement  |





sidered unlikely that the lack of reaction to dihydrostreptomycin represented merely a loss of drug "hypersensitivity" with the passage of time. Thus it appears that dihydrostreptomycin is sufficiently different from streptomycin to allow its use in persons who are hypersensitive to the latter drug.

It should be noted, however, that dihydrostreptomycin might itself produce manifestations of hypersensitivity. In one patient (Case 2) treated with the "crude" preparation, urticaria appeared on the second day of therapy.

*Eosinophilia:* The appearance of eosinophilia, which is believed to be related to drug sensitivity, was a common occurrence in patients receiving both "crude" and "purified" dihydrostreptomycin. In 6 of 9 previously untreated patients who received dihydrostreptomycin for more than sixteen days, eosinophilia of 5 to 16 per cent was observed. Moreover, this phenomenon was noted in one patient (Case 10) who received only the "purified" preparation of dihydrostreptomycin.

#### OTHER MANIFESTATIONS OF TOXICITY

*Renal Toxicity:* Dihydrostreptomycin has produced some degree of renal damage in 3 of 5 patients who received 5.0 Gm. daily of the "crude" preparation for periods of more than thirty days. This complication proved fatal in one patient (Case 4) who developed albuminuria on the twenty-sixth day, an elevated blood urea nitrogen on the thirty-ninth day (46 mg. per 100 cc.) and died in uremia on the fifty-fourth day, nine days after the cessation of chemotherapy. Lower nephron nephrosis was revealed at postmortem examination.

FIG. 3. This patient's course illustrates the absence of manifestations of hypersensitivity to dihydrostreptomycin in a patient who was still hypersensitive to streptomycin. R. Sm. was a sixty-five-year-old man with subacute bacterial endocarditis due to *Streptococcus fecalis*. After failure to control the infection with large doses of penicillin, he was given streptomycin. Because of fever and a generalized maculopapular eruption, the drug was discontinued early on the thirteenth day. On the fourteenth day he was markedly improved, but all the previous symptoms were reproduced that evening by another dose of streptomycin. As indicated, subsequent doses of dihydrostreptomycin were well tolerated without untoward reaction.

FIG. 4. This chart illustrates the absence of toxic reaction to dihydrostreptomycin in a patient (Gia.) with hypersensitivity to streptomycin. The reaction to streptomycin, which consisted of fever, marked malaise and vomiting, was reproduced on the twelfth and seventeenth days by small doses of two other highly purified streptomycin salts. Two doses of dihydrostreptomycin caused no symptoms or fever on the fifteenth and sixteenth days.

FIG. 5. Effects of dihydrostreptomycin in a patient (Case 11, R. Pi.) with drug fever due to streptomycin. This thirty-six-year-old housewife had far advanced pulmonary tuberculosis, as well as laryngeal, buccal and cutaneous tuberculosis. Streptomycin had been applied topically to a sublingual ulcer for six months prior to admission, and the initial intramuscular dose was followed by malaise, urticaria, chill and fever. Milder reactions occurred after smaller doses, including one of a different streptomycin salt. As may be seen, the initial dose of dihydrostreptomycin was given at a time the patient had fever which was considered to be due to her extensive pulmonary disease. The severe systemic symptoms previously caused by streptomycin, however, did not occur following administration of the dihydro derivative, and a subsequent test dose of streptomycin did reproduce this reaction. As might be expected, the hypersensitivity to streptomycin did not persist and had disappeared on the forty-eighth day. As may be seen in this chart and in figure 8, a satisfactory clinical result was obtained.

Another patient (Case 3) had had transient albuminuria before treatment. Persistent slight albuminuria reappeared on the twenty-eighth day, but he presented no other evidence of renal damage during the remaining nine days of treatment or thereafter. In one patient (Case 6), who had diabetes and hypertension, a rise in blood urea nitrogen from 14 to 31 mg. per 100 cc. was noted on the twenty-seventh day of chemotherapy. Treatment was discontinued on the thirty-second day. The following day, his blood urea nitrogen fell to 12 mg. per 100 cc. and a urea clearance test revealed normal values. No other patient has showed any evidence of renal damage.

*Local Irritation:* The intramuscular injection of "purified" dihydrostreptomycin in 1.0 Gm. doses has caused little discomfort. Three patients, not in the present series, were given one dose each. They had been receiving highly purified streptomycin sulfate in 1.0 Gm. doses and were unable to distinguish between the compounds injected.

"Crude" dihydrostreptomycin in individual intramuscular injections of 1.0 Gm. caused moderate to severe local pain and tenderness and occasionally necessitated temporary interruption of therapy. Three patients (Cases 1, 2, 6) who were receiving 5.0 Gm. of the "crude" material daily, eventually developed sterile abscesses of the buttock which responded well to conservative management.

*Incidental toxic reactions:* Most of the patients receiving dihydrostreptomycin experienced mild, tingling paresthesias of the finger tips and about the mouth. There was no significant discomfort from this reaction.

Four patients receiving 5.0 Gm. of "crude" dihydrostreptomycin had nausea. It was transient in 3 cases, appearing on the second, thirty-first, and sixtieth days, respectively. Nausea appeared on the thirteenth day in the other patient (Case 4) and grew progressively worse with anorexia, constipation and abdominal distress.

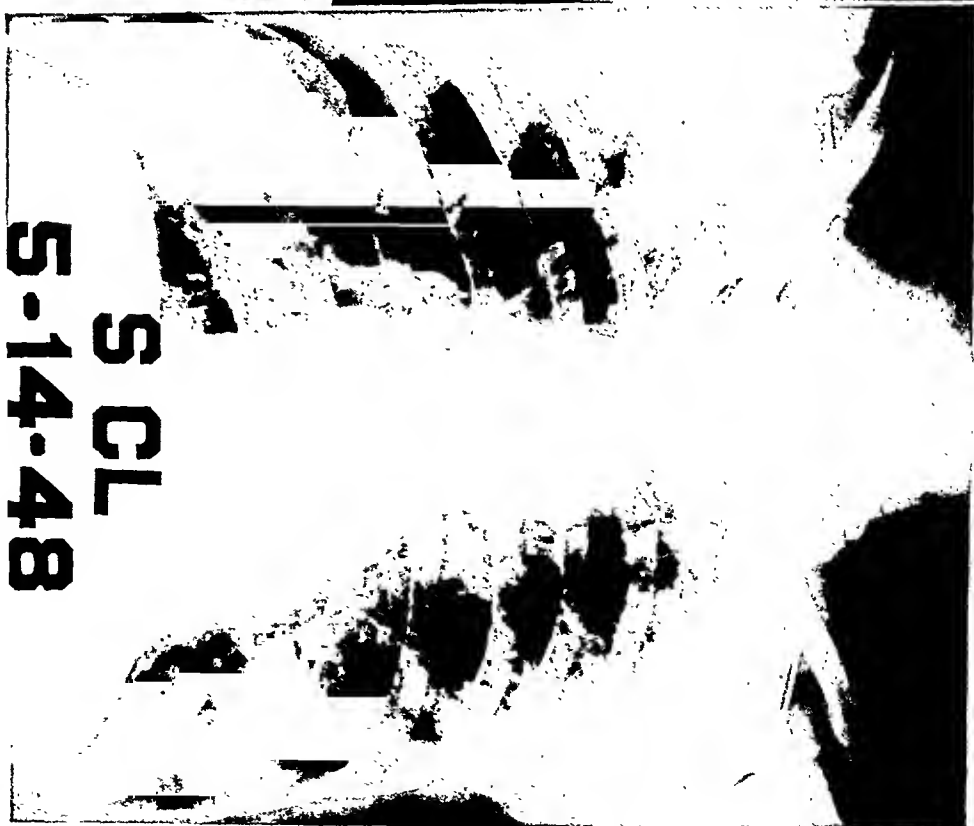
In no case was there evidence of depression of hematopoietic activity, and liver function was not obviously damaged by the medication, even in the 2 patients with cirrhosis.

#### THERAPEUTIC EFFECTIVENESS OF DIHYDROSTREPTOMYCIN

A precise comparison of the respective antimicrobial activities of streptomycin and its dihydro derivative in the treatment of tuberculosis probably can best be obtained by suitable experiments in animals. All that it is possible to report on the present series of 12 tuberculous patients treated with dihydrostreptomycin is the impression of the clinical investigators (table 4). It was believed that the changes in the course of the tuberculous infections during treatment were at least as marked as had been previously observed from the administration of streptomycin (20, 21, 22). One patient with acute generalized hematogenous tuberculosis experienced an early remission of the evidences of infection. In 2 patients, extensive tuberculous ulcerations of the pharynx and larynx healed promptly and in several patients a striking degree of roentgenographic "clearing" was observed (figures 6, 7, and 8).



6a



6b

Fig. 6a. Pretreatment roentgenogram of a forty-nine-year-old white printer (Case 2) who had had a cough for three years. Three weeks prior to this film, he had several hemoptyses with a spread of the pulmonary disease, and large numbers of tubercle bacilli were found in the sputum.

Fig. 6b. Roentgenogram of the same patient (Case 2) on the seventieth day of treatment with 5.0 Gm. of dihydrostreptomycin daily. There was considerable improvement in the areas of recent spread, but numerous cavities became evident in both upper lobes. He remained slightly febrile with a positive sputum, and a new lesion appeared in the left lower lobe three weeks after dihydrostreptomycin was discontinued.

12967

J ST  
8-27-48

Fig. 7b

J ST  
7-1-48

Fig. 7a

Relapse, which has been not infrequent after the streptomycin treatment of pulmonary tuberculosis, has also been observed in 3 of the 12 cases treated with dihydrostreptomycin.

The patient (Case 4) who died from renal damage on the fifty-fourth day had had marked improvement in the roentgenographic appearance of the lungs during treatment. On section, the lungs showed many large cavities which were mostly thin-walled. Although some of these contained necrotic material, there was very little tuberculous tissue, and no tubercle bacilli were obtained on culture.

One patient (Case 5) died on the sixteenth day of therapy. She had very extensive pulmonary tuberculosis, both old and recent, and a recent generalized, hematogenous dissemination. She was also a chronic alcoholic with hepatic cirrhosis. Although her temperature fell from 39.5°C to about 38°C. during treatment with dihydrostreptomycin, there was no other sign of improvement and she died on the sixteenth day. Sections of the lungs showed no evidence of recent healing.

#### RESISTANCE OF M. TUBERCULOSIS TO DIHYDROSTREPTOMYCIN AND STREPTOMYCIN

Tubercle bacilli were isolated from the sputum or gastric aspirate of patients treated with dihydrostreptomycin and tested for sensitivity to that compound and to streptomycin. The methods previously described (20) were followed, except that serial ten-fold dilutions of the compounds were used for all but a few of the sensitivity tests. In table 6 may be seen the times that cultures were made in relation to the treatment and a summary of the results.

In this small series of patients, resistant strains of tubercle bacilli appeared as would be expected during treatment with streptomycin. Every strain which was highly resistant to one compound, *i.e.*, not inhibited by 1,000 micrograms per cc., was resistant to the other. Strains which were inhibited by low concentrations per cc. of streptomycin were also inhibited by low concentrations of dihydrostreptomycin.

#### DISCUSSION

From the above observations it appears that, insofar as tested, the pharmacologic and antibacterial characteristics of dihydrostreptomycin and streptomycin are qualitatively similar but that certain quantitative differences between the two compounds may be of importance. Virtually all of the important toxic reactions produced by streptomycin can be produced by the dihydro derivative. Thus, in the larger dosages employed in this study, dihydrostreptomycin caused

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FIG. 7a. Pretreatment roentgenogram of a thirty-one-year-old white bus driver (Case 9) who had had an abrupt onset of cough and fever one and a half months prior to this film. There were signs of consolidation over the extensive lesion in the right upper lobe, and smaller infiltrated areas could be seen throughout the right lung field. Many tubercle bacilli were present in the sputum.

FIG. 7b. Roentgenogram of J. St. (Case 9) on the fortieth day of treatment with 3.0 Gm. of dihydrostreptomycin daily. At this time tubercle bacilli could no longer be cultured from his sputum, his sedimentation rate had become normal, and he was asymptomatic. The chest lesions were found to be markedly improved by roentgenography and by physical examination. Improvement has continued after completion of forty-two days of treatment.



Fig. 8a. Pretreatment roentgenogram of a thirty-six-year-old white housewife (Case 11) with long-standing tuberculosis of the larynx, lungs, mouth and skin. An extensive bronchogenic dissemination was found three months prior to this film, and had gradually become more evident despite bed-rest. The chronic lesions in both upper lobes are not well shown in this roentgenogram. She was febrile (39.4° C.) and gravely ill at this time. Improvement has continued since antimicrobial therapy was discontinued. See figure 5 for the clinical course.

Fig. 8b. Roentgenogram of R. Pi. (Case 11) after forty-five days of treatment with 1.0 Gm. of dihydrostreptomycin daily. At this time there was considerable improvement in the tuberculosis of the larynx, mouth, and skin, as well as roentgenographic clearing. See figure 5 for the clinical course.

vestibular dysfunction, hearing loss, renal damage, and eosinophilia. Dihydrostreptomycin, however, seems to be distinctly less neurotoxic than streptomycin, as judged by the length of therapy and the total dose of each required to produce the "dizziness" characteristic of vestibular dysfunction. This symptom has usually been the first evidence of vestibular dysfunction in patients receiving large doses of streptomycin (12, 19, 22). In earlier studies on this service, it was

TABLE 6

*Sensitivity of M. tuberculosis to dihydrostreptomycin and streptomycin during treatment with the former*

| PATIENT AND TREATMENT  | TIME OF CULTURE<br>(DAY AFTER START OF TREATMENT) | SENSITIVITY (MICROGRAMS CC) |              |
|--|---|-----------------------------|--------------|
|  |   | Dihydrostreptomycin         | Streptomycin |
| 1. G. Sc., 5.0 Gm. for 78 days.<br>(previously treated with SM,† 1 Gm., 8/8 to 9/17 and 10/29 to 12/9/47). | Before DHSM* (11/18)                              |                             | >1,000       |
|  | Before DHSM (12/16)                               | 3.12                        | 1.56         |
|  | Before DHSM (one week)                            |                             | 10-100       |
|  | 20 days   |                             | >1,000       |
|  | 48 days   |                             | >1,000       |
|  | 76 days   | >1,000                      | >1,000       |
|  | 145 days  | >1,000                      | >1,000       |
| 2. S. Cl., 5.0 Gm. for 73 days.  | Before DHSM (two weeks)                           |                             | <1           |
|  | Before DHSM (one day)                             | 0.625                       | 0.625        |
|  | 28 days   |                             | <1           |
|  | 56 days   | >1,000                      | >1,000       |
|  | 97 days   | >1,000                      | >1,000       |
| 4. C. Ve., 5.0 Gm. for 45 days.  | Before DHSM (one week)                            | 1.25                        | 1.25         |
|  | 12 days   |                             | 1-10         |
|  | 26 days   | 0.625                       | 0.625        |
| 5. A. Fl., 5.0 Gm. for 16 days.  | Before DHSM (three days)                          | 0.625                       | 0.625        |
|  | 17 days (postmortem)                              | 0.312                       | 0.625        |
| 11. R. Pi., 1.0 Gm. for 46 days,<br>then SM, 1.0 Gm. for 47 days.  | Before DHSM (three weeks)‡                        |                             | <1           |
|  | 11 days   |                             | <1           |
|  | 26 days   | 1.25                        | 1.25         |
|  | 153 days  | 3.12                        | 3.12         |

\* DHSM—dihydrostreptomycin.

† SM—streptomycin.

‡ Streptomycin had been topically applied to buccal ulcer for 6 months at this time.

observed that 37 of 38 patients became "dizzy" when treated for ninety days with 3.0 Gm. of streptomycin daily in eight intramuscular injections. This occurred about the twentieth day of treatment (day of onset  $\pm$  S.D. =  $19.75 \pm 2.5$  days) when a total of about 60 Gm. had been given. In contrast, dihydrostreptomycin produced "dizziness" first on the forty-second day after a total of 176 Gm., and in other patients on the forty-fourth and sixty-first days after total doses of 195 and 270 Gm. respectively. It should be noted, however, that the caloric response was absent on the thirty-second and thirty-third days in 2 patients who never were "dizzy". The total doses of dihydrostreptomycin in these 2 patients were 166 and 96 Gm.



It thus appears that neurotoxicity, as indicated by the symptoms and signs of vestibular dysfunction, is manifested later and after a larger total dose with 5.0 Gm. of dihydrostreptomycin daily than with 3.0 Gm. of streptomycin daily.

Dihydrostreptomycin can also produce damage to the auditory apparatus similar to the toxic effect of streptomycin. Although a comparison of the toxicity of the two compounds on the auditory apparatus is difficult, the observations thus far indicate that dihydrostreptomycin is no more toxic and may prove to be significantly less toxic in this respect than streptomycin.

Renal damage, which has been observed in patients receiving streptomycin (19) also occurred in those getting dihydrostreptomycin. The three patients in this study who showed renal damage had received very large doses of the "crude" preparation. It is worthy of note that, in addition to the active drug, these patients received large doses of impurities, the renal toxicity of which is not known. No evidence of renal dysfunction has been observed with 3.0 Gm. or less of dihydrostreptomycin daily.

Although the local reactions at the site of injection of the crude preparations of dihydrostreptomycin were frequently severe, the purified preparations used in this study have not caused local reactions. In view of the lower neurotoxicity of dihydrostreptomycin, it will be of particular interest to determine whether the purified preparations of dihydrostreptomycin are any less toxic than streptomycin when given intrathecally<sup>6</sup>.

In addition to the quantitative differences between dihydrostreptomycin and streptomycin, at least one qualitative difference was noted. Five patients with readily demonstrable hypersensitivity to streptomycin tolerated dihydrostreptomycin in doses as high as 2.0 Gm. daily without untoward reaction. Dihydrostreptomycin should be useful, therefore, in the few patients in whom this type of reaction develops when interruption of treatment is undesirable.

It should be emphasized that, although the toxicity of streptomycin is well known, there is as yet little information in humans on the therapeutic effectiveness of streptomycin in very low doses. Hence the precise relation of toxic dose to optimal therapeutic dose of streptomycin has not yet been established. It is thus of considerable importance that experience be gained on the therapeutic effectiveness of dihydrostreptomycin in dosages which are well tolerated for prolonged periods.

#### SUMMARY

Dihydrostreptomycin is a compound which is derived from streptomycin and which has the same range of antimicrobial activity. The present study indicates that the toxicity of dihydrostreptomycin differs significantly from that of streptomycin. Both drugs may cause a variety of toxic reactions in humans when administered over long periods and the reactions of dihydrostreptomycin, when they occur, are in all respects similar to those caused by the parent compound. Dihydrostreptomycin, however, was found to be less neurotoxic than strepto-

<sup>6</sup> Since this manuscript was submitted for publication, one patient with tuberculous meningitis has received six intrathecal injections of 0.05 Gm. of purified dihydrostreptomycin sulfate. Thus far no untoward reaction has been observed, and the evidences of local irritation have been no greater than those noted following intrathecal administration of purified streptomycin sulfate.

mycin. In the patients treated in this study, evidence of vestibular damage appeared later and less uniformly with 5.0 Gm. of dihydrostreptomycin daily than it has in patients given 3.0 Gm. of streptomycin daily. The disability resulting from vestibular dysfunction has likewise been less than that seen with the latter treatment. Moreover, although dihydrostreptomycin may cause damage to the auditory apparatus, it is no more toxic in this respect than streptomycin and, in all probability, is less so.

Dihydrostreptomycin is also well tolerated by patients who are hypersensitive to streptomycin. Five patients were given the dihydro derivative in doses up to 2.0 Gm. daily without any untoward reaction at times when hypersensitivity to streptomycin was readily demonstrable.

In the twelve cases of pulmonary tuberculosis reported here, the therapeutic results were judged to be as good as those that have been obtained with streptomycin. Resistant strains of tubercle bacilli have emerged during treatment with dihydrostreptomycin in the same fashion as with streptomycin. Highly resistant strains, not inhibited by 1,000 micrograms per cc. of one compound, are similarly resistant to the other.

Dihydrostreptomycin, therefore, should prove to be useful in the treatment of patients unable to tolerate streptomycin because of hypersensitivity. The lower neurotoxicity of the dihydro derivative also suggests that it is preferable to streptomycin for the treatment of patients who require large doses or long courses of the antibacterial agent.

#### SUMARIO

##### *Investigación de la Dihidroestreptomicina en el Laboratorio y en la Clínica*

La dihidroestreptomicina es un compuesto derivado de la estreptomicina y dotado de la misma escala de actividad antimicrobiana. El estudio actual indica que la toxicidad de la dihidroestreptomicina discrepa en forma significativa de la estreptomicina. Ambas drogas pueden ocasionar varias reacciones tóxicas en los seres humanos al ser administradas durante períodos prolongados, y las reacciones a la dihidroestreptomicina, cuando se presentan, son en todos sentidos semejantes a las producidas por el compuesto primario. Sin embargo, la dihidroestreptomicina resultó ser menos neurotóxica que la estreptomicina. En los enfermos tratados en este estudio, aparecieron signos de lesión vestibular más tarde y menos constantemente con 5.0 gramos diarios de dihidroestreptomicina que lo observado con 3.0 gramos diarios de estreptomicina. La incapacidad debida a la disfunción vestibular también fué menor. Además, aunque la dihidroestreptomicina puede afectar el aparato auditivo, no es más tóxica en este sentido que la estreptomicina, y con toda probabilidad, lo es menos.

La dihidroestreptomicina es también bien tolerada por los enfermos hipersensibles a la estreptomicina. Cinco enfermos la recibieron a dosis hasta de 2.0 gramos diarios sin la menor reacción adversa en ocasiones en que la hipersensibilidad a la estreptomicina se hallaba bien patente.

En los doce casos de tuberculosis pulmonar descritos ahora, los resultados terapéuticos se consideraron tan buenos como los obtenidos con la estreptomicina. Durante el tratamiento con la dihidroestreptomicina, han aparecido cepas resistentes de bacilos tuberculosos de la misma manera que con la estreptomicina.

Cepas muy resistentes, que no inhiben 1000 microgramos de un compuesto por cc., son igualmente resistentes al otro.

La dihidroestreptomycin debe, por lo tanto, resultar útil en el tratamiento de los pacientes que no pueden, debido a la hipersensibilidad, tolerar la estreptomycin. La menor neurotoxicidad del derivado también indica que es preferible a la estreptomycin para el tratamiento de los enfermos que exigen dosis grandes o series prolongadas de este elemento antibacteriano.

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# THE CLINICAL ADMINISTRATION OF DIHYDOSTREPTOMYCIN IN TUBERCULOSIS

## A Preliminary Report

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### INTRODUCTION

It has been predicted on many occasions during the past eight years that an ever increasing series of clinically useful drugs would appear as a result of the growing interest in antibacterial drug therapy of tuberculosis. The first of these drugs was "promin" (a derivative of diaminodiphenylsulfone), which appeared in 1940 and is still being utilized clinically. When streptomycin was developed in 1944, it was found to be less toxic and more effective than promin or any of the other antituberculosis drugs. It now has become recognized as an indispensable aid to the medical and surgical treatment of many types of tuberculosis.

Two principal handicaps to more widespread utilization of streptomycin in tuberculosis have appeared: (1) the frequent emergence of streptomycin-resistant strains of tubercle bacilli; and (2) toxic manifestations produced by streptomycin which frequently are uncomfortable and at times are severe and disabling.

Neurotoxic manifestations of streptomycin therapy are almost uniformly observed in patients when larger doses (40 mg. or more per kg. of body weight per day) are administered for a few weeks. These reactions were described in the first reports concerning streptomycin therapy in clinical tuberculosis (1). Most prominent among these toxic reactions is the damage to the vestibular function of the eighth cranial nerve. When the daily dose of streptomycin is reduced (to less than 20 mg. per kg. of body weight), these symptoms are observed in only a minority of patients treated, but it is not always possible to predict which patients will be affected. Many physicians believe that these lower dosage ranges are equally effective in the treatment of tuberculosis, especially those types of tuberculous disease which respond most promptly to specific therapy. It has not been demonstrated conclusively, however, that these lower dosage levels are adequate to meet some clinical situations in which the patient might be benefited by larger doses. Furthermore, many physicians have expressed the need for a drug with a wider margin of safety than is offered by streptomycin.

Accordingly, an investigation to determine the clinical possibilities of dihydrosstreptomycin<sup>4</sup> was undertaken early in 1948, after the effectiveness of the drug against experimental tuberculosis had been demonstrated during the previous

year in this institution (2). Although the number of patients treated remains small, the results have been sufficiently uniform to justify the publication of this preliminary report and to indicate that dihydrostreptomycin possesses certain advantages over streptomycin for the treatment of tuberculosis.

#### CLINICAL INVESTIGATION

Dihydrostreptomycin has been administered to 14 patients, 13 of whom were suffering from tuberculosis of various types, as indicated in table 1. The table also indicates the amounts of dihydrostreptomycin administered and the results observed. If similar doses of streptomycin had been administered, it is believed that in most of these cases symptoms of drug toxicity would have developed. The dihydrostreptomycin utilized in these studies was of a purified type which the manufacturers stated was comparable in purity to present-day commercial streptomycin.

#### TOXICITY OF DIHYDROSTREPTOMYCIN

*Neurotoxic manifestations:* The only case in which any evidence of severe nerve damage developed was case 14 (table 1), in which the patient first received 2.8 gm. of streptomycin per day for eight days and the usual early and acute evidences of vestibular nerve damage produced by streptomycin developed. After a lapse of fourteen days, streptomycin treatment was attempted again but was discontinued after three days (2.0 gm. per day) because of severe vertigo. Six weeks later, 3.2 gm. of dihydrostreptomycin per day were administered. After twenty days of such treatment, severe dizziness was noted. The labyrinths reacted normally to caloric stimulation before dihydrostreptomycin treatment was started and were very sluggish after treatment was completed. It should be mentioned also that this patient manifested renal insufficiency with an elevation of the level of blood urea (to 140 mg. per 100 cc. of blood) and that an estimation of dihydrostreptomycin content of blood serum yielded the extremely high level of 320 micrograms per cc. of serum. Nevertheless, the observations afford evidence that dihydrostreptomycin may produce neurotoxic phenomena, provided sufficiently high blood levels are attained.

A second patient (Case 2) developed mild symptoms of vestibular dysfunction after forty-two days of treatment with dihydrostreptomycin (3.0 gm. per day). Treatment was discontinued and symptoms disappeared within a week, but caloric tests revealed moderate hypoactivity of the vestibular apparatus.

In no other case did any subjective or objective evidence of nerve damage develop. No other patient complained of dizziness, vertigo, tinnitus, deafness, paresthesias or visual difficulties. Tests of vestibular function, utilizing the quantitative caloric method of Kobrac, were done on all patients during treatment (usually every two weeks) and at the conclusion of treatment (except for case 6, in which treatment was completed elsewhere).

*Allergic manifestations:* It has long been suspected (3) that there may be some relation between allergy to streptomycin, vestibular dysfunction, and the eosinophilia which is so frequently observed during streptomycin treatment.

TABLE 1  
*Clinical data on tuberculous patients treated with dihydrostreptomycin*

| CASE | DIAGNOSIS   | DOSE, GM.<br>PER DAY<br>DIHYDRO-<br>STREPTO-<br>MYCIN | DAYS<br>TREATED | OTHER SPECIFIC THERAPY  | APPARENT THERAPEUTIC<br>EFFECTS                | SYSTEMIC TOXIC EFFECTS  |
|------|---|---|-----------------|---|--|---|
| 1    | Pulmonary tuberculosis                            | 2.0   | 60              | None  | Good   | None  |
| 2    | Tuberculous sinuses of chest wall                 | 3.0   | 42              | None  | Excellent                                      | Mild vestibular dysfunction   |
| 3    | Pulmonary tuberculosis after lobec-<br>tomy       | 2.0   | 60              | None  | No postoperative<br>complication               | None  |
| 4    | Tuberculous abscess of shoulder                   | 1.0   | 22              | PAS,* average 0.0   | Excellent                                      | None  |
| 5    | Pulmonary tuberculosis                            | 2.0   | 42              | gm. per day   | Excellent                                      | None  |
| 6    | Pulmonary tuberculosis                            | 1.0   | 42              | None  | Questionable                                   | None  |
| 7    | Tuberculous meningitis                            | 2.0   | 60              | None  | Excellent                                      | Spinal block, irritation after 2 intra-<br>thecal injections (50 mg. each)                        |
|      |   | 2.0   | 120             | PAS,* average 10<br>gm. per day;<br>streptomycin<br>2.0 gm. (1<br>week) |  |   |
| 8    | Tuberculous meningitis                            | 3.0   | 38              | 7 intrathecal in-<br>jections   | Questionable and<br>temporary.<br>Patient died | Marked irritation after intrathecal<br>administration of dihydrostrepto-<br>mycin                 |
| 9    | Tuberculous meningitis                            | 3.0   | 10              | Promin I.V. 5.0<br>gm. per day  | None   | Comatose and toxicity could not be<br>determined  |
| 10   | Miliary tuberculosis                              | 3.0   | 60              | PAS,* 0.0-10.0<br>gm. per day;<br>promin I.V. 5.0<br>gm. per day        | Good   | None  |
| 11   | Postoperative tuberculous empyema                 | 1.0   | 25              | None  | Poor; streptomycin-<br>resistant<br>bacilli    | Streptomycin produced exfoliative<br>dermatitis. Dihydrostreptomycin<br>tolerated well (see text) |
| 12   | Tuberculous dacrylitis, lupus vul-                | 1.0   | 60              | None  | Good   | None  |
| 13   | <sup>Farris</sup><br>Pulmonary tuberculosis       | 2.0   |                 | PAS*  |  | Vestibular damage progressed dur-   |
| 14   | Staphylococcal bacteremia, renal<br>insufficiency | 3.2   | 26              | Streptomycin, 2.8<br>gm., 12 days                                       |  | ing dihydrostreptomycin therapy   |

\* PAS—Abbreviation for para-aminosalicylic acid.

Repeated differential blood counts (usually once each week) were carried out on all patients receiving dihydrostreptomycin. In no instance did any eosinophilia develop in excess of 5 per cent.

In no case did any drug rash or other evidence of allergic response to dihydrostreptomycin develop. One patient (case 11), who was highly sensitive to streptomycin (manifested by drug fever and exfoliative dermatitis), tolerated dihydrostreptomycin without any difficulty.

*Other observations on toxicity:* Studies of liver function were carried out in 10 of these patients during the course of dihydrostreptomycin therapy (sulfobromophthalein sodium dye retention test and cephalin-cholesterol flocculation test) and no evidence of hepatic damage due to treatment was revealed. Repeated urinalyses and blood urea determinations showed no abnormality that could be attributed to dihydrostreptomycin. Hemoglobin estimations, erythrocyte and leukocyte counts, and differential blood counts were performed periodically (usually once each week) and no evidence of damage to the hematopoietic system by dihydrostreptomycin was obtained. There were no gastro-intestinal symptoms which could clearly be attributed to dihydrostreptomycin therapy, although two patients (cases 7 and 10) complained of abdominal distress with gaseous dyspepsia which was relieved when treatment was stopped.

*Irritation at the injection site:*<sup>6</sup> The dihydrostreptomycin utilized in these studies appeared to cause somewhat more pain and soreness at the site of intramuscular injection than is customarily observed from the administration of streptomycin on this service. Patients who have received both drugs agree that this dihydrostreptomycin was more irritating than streptomycin. In no instance was it considered necessary to discontinue the regular administration of the drug because of these reactions.

*Irritation produced by intrathecal injection:* Each of the 3 patients who had tuberculous meningitis (cases 7, 8 and 9) received dihydrostreptomycin intrathecally in doses of 50 mg. every forty-eight hours. In each instance it was necessary to discontinue intrathecal therapy after two to fourteen injections because of evidence of spinal cord irritation and cerebrospinal fluid block. Patient 7 has experienced an excellent clinical remission, although he has received only two injections of dihydrostreptomycin (50 mg. each) intrathecally and six injections of streptomycin (50 mg. each) by this route, in addition to the intramuscular injections indicated in table 1. A fourth patient with tuberculous meningitis, who is not listed in table 1, received dihydrostreptomycin intrathecally and streptomycin intramuscularly. The usual symptoms of vestibular dysfunction, apparently as a result of the streptomycin, developed, as well as very severe reactions from the fourteen intrathecal injections of dihydrostreptomycin which he received. The latter reactions resulted in partial paraplegia, urinary incontinence, fecal incontinence and a "saddle" type of cutaneous anesthesia. After a partial clinical remission of several weeks, his symptoms of meningitis recurred and he died.

\* Since the preparation of this manuscript, recent lots of dihydrostreptomycin received from the same manufacturer have apparently produced no more irritation at the injection site than is usually observed following injections of similar amounts of streptomycin.

The intrathecal injection of dihydrostreptomycin is not recommended unless a method is found to reduce this apparent factor of chemical irritation.

#### SUMMARY AND CONCLUSIONS

Sufficient evidence has been accumulated to indicate that dihydrostreptomycin is an effective drug for the treatment of some types of clinical tuberculosis. Its activity is probably similar to that of streptomycin but it is clearly much less toxic than streptomycin when given in comparable doses for similar periods. Most significant is the fact that dihydrostreptomycin may be administered to patients in doses of 2.0 to 3.0 gm. per day for sixty days, or perhaps longer, with little danger of producing impairment of function of the organs of equilibration.

The fact that dihydrostreptomycin may be administered to some patients who are markedly allergic to streptomycin and the fact that eosinophilia has not been observed in this series of treated patients may be important.

The only unfavorable attribute of dihydrostreptomycin which was noted was irritation of the tissues at the site of injection. The irritation is appreciably more severe than that produced by streptomycin. Intrathecal injection of dihydrostreptomycin is not recommended for the treatment of meningitis unless a less irritant form of the drug can be produced. Patients with meningitis treated with dihydrostreptomycin might be given purified streptomycin intrathecally.

The series of patients reported on here is not sufficiently large, nor is the period of observation sufficiently long, to have revealed all of the possible toxic potentialities of dihydrostreptomycin.

#### SUMARIO Y CONCLUSIONES

##### *La Administración Clínica de Dihidroestreptomicina en la Tuberculosis. Informe Preliminar*

Ya se han acopiado suficientes datos indicativos de que la dihidroestreptomicina es una droga eficaz para el tratamiento de algunas formas de tuberculosis clínica. Su actividad es probablemente semejante a la de la estreptomicina, pero es manifiestamente mucho menos tóxica cuando se administra a dosis comparables durante períodos de tiempo semejantes. De lo más importante es que puede administrarse a dosis de 2.0 a 3.0 gm. diarios durante 60 días, y quizás más, con poco o ningún riesgo de afectar la función de los órganos del equilibrio.

Pueden revestir importancia el hecho de que puede administrarse dihidroestreptomicina a algunos enfermos que son decididamente alérgicos a la estreptomicina y el hecho de que no se ha observado eosinofilia en esta serie de enfermos tratados.

El único atributo contraproducente de la dihidroestreptomicina que se observara consistió en irritación de los tejidos en el sitio de la inyección. Esa irritación fué apreciablemente más intensa que la producida por la estreptomicina. Hasta que se obtenga una forma menos irritante de la droga, no se recomienda la inyección intratecal de dihidroestreptomicina para el tratamiento de la meningi-



tis. Los meningíticos tratados con dihidroestreptomicina pueden recibir por vía tecal estreptomicina purificada.

La serie de pacientes aquí descrita no es suficientemente numerosa ni el período de observación suficientemente largo para revelar todas las posibles potencialidades tóxicas de la dihidroestreptomicina.

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# THE DISTRIBUTION OF DIHYDROSTREPTOMYCIN IN VARIOUS BODY FLUIDS

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## INTRODUCTION

The preparation of dihydrostreptomycin<sup>5</sup> by the catalytic reduction of streptomycin was described independently by Peck and co-workers (1), Bartz and co-workers (2), and Fried and Wintersteiner (3). This compound was found to be more stable than streptomycin by the foregoing workers, and Youmans (4) and Donovan and Rake (5) found it to be effective *in vitro* against the H37Rv strain of tubercle bacilli. Feldman and his associates (6) found this drug to be as effective as streptomycin against experimental tuberculosis in guinea pigs, and preliminary studies by Hinshaw and his co-workers (7) seemed to show that dihydrostreptomycin suppressed tuberculosis in man to about the same degree as did streptomycin.

In contrast to streptomycin, the usual doses of dihydrostreptomycin did not cause vertigo to develop. Therefore, it seemed wise to study the concentrations of dihydrostreptomycin in the blood and the other body fluids in order to determine if the absence of symptoms of neurotoxicity was due to low concentrations of the drug.

The determinations were performed by a modification of the cup plate method of assay (8). The test organism used was the SM strain of *Staphylococcus aureus*. The drug was always given intramuscularly in a concentration of 0.2 gm. per cc. of distilled water.

## OBSERVATIONS

### *Concentration of Dihydrostreptomycin in the Blood*

In tables 1, 2 and 3 may be seen the concentration of dihydrostreptomycin in the blood serum at various time intervals after the intramuscular injection of different doses of the drug. It will be seen that the concentration is greatest about one hour after the injection and then gradually falls. Significant quantities of the drug are found in the blood, however, for twenty-four hours after the intramuscular injection of either 1.0 or 2.0 gm.

### *Placental Transmission of Dihydrostreptomycin*

In table 4 may be seen the concentration of dihydrostreptomycin in the maternal and fetal bloods at varying intervals after the intramuscular injection of 1.0

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<sup>5</sup> The dihydrostreptomycin utilized in these studies was supplied by Merck & Co., Inc. Rah way, New Jersey, through Dr. J. M. Carlisle and Dr. A. Gibson.

gm. of the drug. The drug passed through the placental membrane in significant quantities, although in no case was the concentration in the fetal blood equal to that in the maternal blood.

TABLE 1  
*Dihydrostreptomycin in blood serum of patients receiving 1.0 gm. intramuscularly*

| PATIENT | WEIGHT, KG. | TIME IN HOURS AFTER INJECTION |      |      |      |      |    |    |
|---------|-------------|-------------------------------|------|------|------|------|----|----|
|         |             | 1                             | 6    | 12   | 18   | 24   | 36 | 48 |
| 1       | 55.9        | 47.2*                         | 12.6 | 3.6  | 3.37 | 1.75 | 0  | 0  |
| 2       | 44.5        | 52.8                          | 13.6 | 4.3  | 2.1  | 1.45 | 0  |    |
| 3       | 70.9        | 54.4                          | 8.6  | 3.31 | 1.45 | 0    |    |    |
| 4       | 66.8        | 43.0                          | 39.2 | 4.55 |      | 1.05 |    |    |

\* In micrograms per cc.

TABLE 2  
*Dihydrostreptomycin in blood serum of patients receiving 1.0 gm. intramuscularly every twelve hours*

| PATIENT | WEIGHT, KG. | TIME IN HOURS AFTER LAST DOSE |      |      |      |      |
|---------|-------------|-------------------------------|------|------|------|------|
|         |             | 1                             | 3    | 6    | 8    | 12   |
| 1       | 52.7        | 57.6*                         | 42.4 | 29.2 |      | 15.2 |
| 1       | 52.7        | 56.0                          | 54.9 | 26.4 |      | 11.2 |
| 2       | 60.4        | 45.6                          | 29.6 |      | 10.6 | 4.8  |
| 2       | 60.4        | 54.4                          | 30.4 | 14.4 |      | 6.9  |
| 3       | 97.7        | 40.0†                         | 33.6 | 21.6 |      | 6.8  |

\* In micrograms per cc.

† 1½ hours after last dose.

TABLE 3  
*Dihydrostreptomycin in blood serum of patients receiving 2.0 gm.\* intramuscularly*

| PATIENT | WEIGHT, KG. | TIME IN HOURS AFTER INJECTION |      |      |      |     |      |
|---------|-------------|-------------------------------|------|------|------|-----|------|
|         |             | 1                             | 3    | 6    | 12   | 15  | 24   |
| 1       | 97.7        | 214.4†                        | 70.4 | 31.2 | 10.4 | 7.6 | 3.9  |
| 2       | 60.4        | 119.2                         | 80.6 | 29.6 | 10.0 | 6.6 | 2.5  |
| 3       | 55.9        | 177.6                         | 91.2 | 34.4 | 12.2 | 6.6 | 2.62 |

\* Patients received 1.0 gm. intramuscularly twelve hours prior to start of this study.

† In micrograms per cc.

#### *Dihydrostreptomycin in the Cerebrospinal Fluid*

The concentration of dihydrostreptomycin in the cerebrospinal fluid of patients receiving this drug by intramuscular injection is shown in table 5. Patients 1 and 2 of table 5 were being treated for tuberculous meningitis. These data show that in the presence of tuberculous meningitis dihydrostreptomycin passes through the meninges into the cerebrospinal fluid in significant amounts when

the drug is given by the intramuscular route only. It is not yet known, however, whether dihydrostreptomycin administered solely by the intramuscular route is adequate to control tuberculous meningitis. Experience on this service suggests that dihydrostreptomycin is more irritating to the meninges than is streptomycin. As it is thought that patients with tuberculous meningitis should be treated by both the intramuscular route and the intrathecal route, the practice at present is to administer dihydrostreptomycin intramuscularly and streptomycin intra-

TABLE 4  
*Placental transmission of dihydrostreptomycin*

| CASE | TIME OF INJECTION OF DIHYDROSTREPTOMYCIN* | TIME OF COLLECTION |                | CONCENTRATION OF DIHYDROSTREPTOMYCIN† |                      |
|------|---|--------------------|----------------|---------------------------------------|----------------------|
|      |   | Cord blood         | Maternal blood | Cord blood serum                      | Maternal blood serum |
| 1    | 12:15 a.m.                                | 12:55 a.m.         | 1:20 a.m.      | 7.0                                   | 38.4                 |
| 2    | 4:15 p.m.                                 | 5:58 p.m.          | 6:08 p.m.      | 20.6                                  | 43.6                 |
| 3    | 3:07 a.m.                                 | 3:55 a.m.          | 4:05 a.m.      | 2.4                                   | 22.4                 |

\* Dose, 1.0 gm.

† In micrograms per cc.

TABLE 5  
*Dihydrostreptomycin in cerebrospinal fluid after intramuscular injection*

| PATIENT | DOSE                    | WEIGHT, KG. | TIME AFTER LAST DOSE | CONCENTRATION OF DIHYDROSTREPTOMYCIN* |                     |
|---------|-------------------------|-------------|----------------------|---------------------------------------|---------------------|
|         |                         |             |                      | Blood serum                           | Cerebrospinal fluid |
| 1       | 1.0 gm. every 12 hours  | 56.8        | 30 minutes           | 36.8                                  | 10.4                |
| 2       | 0.25 gm. every 12 hours | 7.7         | 3½ hours             | 20.2                                  | 6.0                 |
| 2       | 0.25 gm. every 12 hours | 7.7         | 2 hours              | 26                                    | 13.1                |
| 3       | 1.0 gm.                 | 84.1        | 18 hours             | 2.0                                   | 1.5                 |
| 4       | 1.0 gm.                 | 88.7        | 20 hours             | 1.5                                   | 1.3                 |
| 5       | 1.0 gm.                 | 59.0        | 21 hours             | 1.05                                  | 1.5                 |
| 6       | 1.0 gm.                 |             | 21 hours             | 1.2                                   | 1.25                |

\* In micrograms per cc.

thecally. Further investigation must be carried out to determine whether or not the intrathecal administration of either drug is necessary.

Patients 3, 4, 5 and 6 of table 5 were being studied for neurosyphilis and had no sign of inflammation of the meninges.

#### *Dihydrostreptomycin in the Pleural Fluid*

The few data in table 6 suggest that dihydrostreptomycin passes freely into the pleural fluid when the drug is given intramuscularly. Patient 1 of table 6 had a bloody pleural effusion probably due to metastatic carcinoma. Patient 2 of table 6 had tuberculous pleurisy with effusion.

*Excretion of Dihydrostreptomycin in the Urine*

The excretion of dihydrostreptomycin in the urine was measured by collecting twenty-four hour samples of urine from patients who were receiving 1.0 gm. of the drug intramuscularly every twelve hours. The data in table 7 show that the drug is excreted in large quantities in the urine, 70 per cent or more of the daily dose being present in each twenty-four hour sample.

## COMMENT

Comparison of these data on dihydrostreptomycin with those presented by Heilman and co-workers (9), Zintel and co-workers (10), Buggs and co-workers

TABLE 6  
*Dihydrostreptomycin in pleural fluid after intramuscular injection*

| PATIENT | WEIGHT, KG. | TIME AFTER INJECTION, HOURS* | CONCENTRATION OF DIHYDROSTREPTOMYCIN† |               |
|---------|-------------|------------------------------|---------------------------------------|---------------|
|         |             |                              | Blood serum                           | Pleural fluid |
| 1       | 53.6        | 18                           | 3.35                                  | 2.75          |
| 2       | 96.3        | 24                           | 3.3                                   | 5.8           |

\* Dose, 1.0 gm.

† In micrograms per cc.

TABLE 7  
*Urinary excretion of dihydrostreptomycin\**

| PATIENT | VOLUME OF URINE IN TWENTY-FOUR HOURS | CONCENTRATION OF DIHYDROSTREPTOMYCIN† | TWENTY-FOUR HOUR EXCRETION |
|---------|--------------------------------------|---------------------------------------|----------------------------|
|         | cc.                                  |                                       | gm.                        |
| 1       | 1,050                                | 1,843.2                               | 1.935                      |
| 2       | 1,595                                | 1,331.2                               | 2.12                       |
| 3       | 1,000                                | 1,408.0                               | 1.4                        |
| 4       | 2,100                                | 844.8                                 | 1.73                       |
| 5       | 1,875                                | 1,126.4                               | 2.11                       |
| 6       | 2,100                                | 665.6                                 | 1.397                      |

\* Dose, 1.0 gm. every twelve hours.

† In micrograms per cc.

(11), and Anderson and Jewell (12) on the distribution of streptomycin suggests that the two drugs are absorbed, distributed, and excreted in a very similar pattern. The greatest concentration of each drug is found in the blood about one hour after intramuscular injection. A satisfactory comparison of the persistence of the two drugs in the blood cannot be made as the concentrations of streptomycin in the blood were followed for a shorter period than the concentrations of dihydrostreptomycin. Anderson and Jewell did find, however, that 2.0 to 5.0 micrograms of streptomycin per cc. were present in the blood serum twelve hours after the intramuscular injection of doses of 0.6 gm. The distribution of the two drugs in the various body fluids seems to be comparable, both

drugs passing into the fetal blood, the pleural fluid, and the cerebrospinal fluid. Both drugs are excreted in the urine in large quantities. The streptomycin studies revealed that up to 90 per cent of the total daily dose was present in a twenty-four hour specimen of urine. The present studies revealed an even higher per cent of dihydrostreptomycin to be present in the urine.

With such large concentration of dihydrostreptomycin in the blood and its presence in all the body fluids studied, it seems likely that the absence of neurotoxicity must be an inherent characteristic of the drug and not due to an inadequate concentration of the drug.

#### SUMMARY

1. After the intramuscular administration of dihydrostreptomycin, the drug was rapidly absorbed into the blood, the greatest concentration being reached in about one hour.

2. Significant quantities of the drug were present in the blood for twenty-four hours after the intramuscular administration of 1.0 or 2.0 gm.

3. The drug passed through the placental membrane and was found in the fetal blood.

4. Dihydrostreptomycin was found in significant quantities in the pleural fluid and the cerebrospinal fluid of patients who had received the drug by intramuscular injection.

5. The drug was excreted in large amounts in the urine, 70 per cent or more of the daily dose being present in each twenty-four hour sample.

6. The absorption, distribution, and excretion of streptomycin and dihydrostreptomycin are very similar.

7. Absence of symptoms of neurotoxicity after intramuscular administration of dihydrostreptomycin cannot be attributed to low concentration of the drug in the blood.

#### SUMARIO

##### *Distribución de la Dihidroestreptomicina en Varios Humores Orgánicos*

1. Después de la administración intramuscular de dihidroestreptomicina la droga fué absorbida rápidamente en la sangre, alcanzándose la concentración máxima aproximadamente en una hora.

2. Hubo presentes en la sangre cantidades significativas de la droga por espacio de 24 horas después de la administración intramuscular de 1.0 ó 2.0 gm.

3. La droga atravesó la membrana placentaria y fué encontrada en la sangre fetal.

4. La dihidroestreptomicina fué descubierta en cantidades significativas en el líquido pleural y el líquido cefalorraquídeo de los enfermos que la habían recibido intramuscularmente.

5. La droga fué excretada en grandes cantidades en la orina, encontrándose 70 por ciento ó más de la dosis diaria en cada muestra de 24 horas.

6. La absorción, distribución y excreción de la estreptomicina y la dihidroestreptomicina son muy semejantes.

7. La falta de síntomas de neurotoxicidad consecutivos a la administración intramuscular de dihidroestreptomicina no puede ser imputada a la baja concentración de la droga en la sangre.

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# THE RESULTS OF SANATORIUM TREATMENT AND COLLAPSE THERAPY

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## INTRODUCTION

Much money is spent by authority and much time by patients in the institutional treatment of pulmonary tuberculosis. Whether the results are good or bad, some expenditure is necessary for the medical care of those who have no resources for such care at home. Moreover, the sanatorium and the methods of active treatment used make some claim to do more than provide simple medical attention. Hence it is desirable to review the results achieved, especially since it is now some years since the researches concerning patients treated at Frimley, Midhurst, Bradford and London have been published. Knowledge of the disease and methods of diagnosis and treatment have so changed during this time that added force is given to the demand for more information on this subject. Diagnosis has become more exact than in the times of previous reports when the help of radiology was not available or was uncertain. Formerly treatment was largely limited to a period spent in a sanatorium, devoted to an active exercise program with short daily periods of rest. Now rest may be adopted for many months and the patient may be subjected to extensive interference by surgical methods, probed by psychologists, and may undergo a careful and lengthy rehabilitation. This last phase bears some relationship to the former sanatorium treatment, but in other ways treatment now includes a much wider range.

It is true that this active policy is not applied to all patients. Physicians have increasingly recognized that many minimal or even some advanced lesions will make good progress to healing without treatment at all. Furthermore, it is appreciated that such a healing process may occur without diagnosis at the time of activity and may be revealed only later by a routine clinical or radiological examination. It is known that a certain group of "good chronics" are able to lead a life of considerable activity and usefulness for many years, though carrying serious lesions in the lungs and expectorating tubercle bacilli. Nevertheless, pulmonary tuberculosis in general remains a serious disease with a high fatality rate. Where tubercle bacilli have been found in the sputum, only a quarter to a third of the patients survive the diagnosis by five years (1, 2, 3, 4).

In England, no estimate of the results of sanatorium treatment of the patients admitted to public sanatoriums has appeared for ten years. Bentley (5) reported the pneumothorax experience of the London County Council and, as a control series, referred to sanatorium patients discharged to that authority and followed for five years. Vallow (6) in Bradford also reported on patients of that city who were not specially selected. In contrast, reports (7, 8) from Frimley and Midhurst indicated that their patients were carefully chosen.

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Since the time of the earlier reports, treatment has been made available through the local authorities for a large proportion of the population. There are now some 25,000 beds available for pulmonary cases, as compared with the relatively few private sanatoriums of forty years ago. It is important to know whether this expenditure on the more extensive provision of institutional treatment has value. In investigating the outcome for patients at Clare Hall, a sanatorium maintained by Middlesex County Council, it is also possible to consider the effect of an increasing use of collapse therapy, in combination with rest and convalescent regimen.

#### CLINICAL MATERIAL

The data for the present investigation are derived from the records of 3,833 persons discharged from Clare Hall County Hospital during the nine years 1937 to 1945. These patients were admitted from the County of Middlesex and were mainly derived from industrial working class or "black-coated" workers and their families. No "distressed areas" existed in the County. Conversely, persons in favourable economic circumstances and those able to pay for their own treatment were rarely admitted. There is a relatively small rural population, most of the inhabitants living in suburban or urban communities.

Active forms of treatment were very little practised before the period of the inquiry, but were introduced in 1937 and have been increasingly employed during subsequent years. Among the patients considered 1,819 (47.5 per cent) underwent collapse therapy, which includes pneumothorax and pneumoperitoneum, evulsion of the phrenic nerve, and major surgical collapse treatment, including thoracoplasty and extrapleural pneumothorax. Simple crushing of the phrenic nerve, unaccompanied by other forms of active treatment, is *not* considered in this paper as collapse therapy and only a very small proportion of the patients received this treatment alone. The classification used is the Ministry of Health grouping (table 1) into TB negative (or A), and TB + 1, TB + 2, and TB + 3 (or B1, B2, and B3). It is assumed that these categories are well known and they have the advantage of being comparable with those in some similar investigations. The distribution of the discharged patients by age, sex, and condition on admission may be seen in table 2.

It was found that a continuous change in the distributions of age, sex and condition on admission took place during the period under review. As a consequence the patients at the end of the nine years were on the average younger and contained a lower proportion with advanced disease, and the sex ratio had been reversed so that a preponderance of males had changed to a greater proportion of females in the discharged patients (tables 3, 4, 5).

The average length of residence in Clare Hall of patients discharged may be seen in table 4. In September 1939 there was premature discharge of a group of patients on account of the outbreak of war, and for this reason also the number of beds available and patients admitted were below normal in 1940. On the whole, however, hospital accommodation was increased, the total number of beds rising from 192 in 1937 to nearly 500 in 1945. The length of stay of patients has been

TABLE 1

*British Ministry of Health classification (pulmonary tuberculosis)*

|                       |  |
|-----------------------|--|
| <i>TB minus (TB-)</i> | Patients in whom tubercle bacilli have never been discovered.  |
| <i>TB plus (TB+)</i>  | Patients in whom tubercle bacilli have at any time been found.   |
| Group 1 (TB + 1)      | Patients with slight or no constitutional disturbance in whom the disease is limited to one lobe or a corresponding amount.  |
| Group 3 (TB + 3)      | Patients with profound systemic disturbance or constitutional deterioration and marked impairment of function, local or general, and with little or no prospect of recovery. This group includes all with grave complications. |
| Group 2 (TB + 2)      | All patients not classified in group 1 or group 3.   |

TABLE 2

| CONDITION ON<br>ADMISSION | MALES            |             |             |             |                |       | FEMALES          |             |             |             |                |       |
|---------------------------|------------------|-------------|-------------|-------------|----------------|-------|------------------|-------------|-------------|-------------|----------------|-------|
|                           | Age on admission |             |             |             |                |       | Age on admission |             |             |             |                |       |
|                           | 15<br>to 24      | 25<br>to 34 | 35<br>to 44 | 45<br>to 54 | 55 and<br>over | Total | 15<br>to 24      | 25<br>to 34 | 35<br>to 44 | 45<br>to 54 | 55 and<br>over | Total |
| TB -                      | 138              | 80          | 54          | 24          | 9              | 305   | 214              | 116         | 32          | 17          | 2              | 381   |
| TB + 1                    | 59               | 31          | 19          | 8           | 2              | 119   | 62               | 34          | 13          | 2           | 3              | 114   |
| TB + 2                    | 300              | 289         | 187         | 108         | 35             | 919   | 324              | 312         | 117         | 25          | 1              | 779   |
| TB + 3                    | 167              | 242         | 161         | 120         | 64             | 754   | 161              | 200         | 67          | 22          | 12             | 462   |
| Total....                 | 664              | 642         | 421         | 260         | 110            | 2,097 | 761              | 662         | 229         | 66          | 18             | 1,736 |

TABLE 3

*Change in age distribution and condition on admission*

| AGES                          | PERCENTAGE DISTRIBUTIONS |              |              |
|-------------------------------|--------------------------|--------------|--------------|
|                               | 1937 to 1939             | 1940 to 1942 | 1943 to 1945 |
| 15 to 24                      | 31.5                     | 32.3         | 43.2         |
| 25 to 34                      | 31.1                     | 38.3         | 32.6         |
| 35 to 44                      | 15.1                     | 16.9         | 17.9         |
| 45 to 54                      | 12.6                     | 10.0         | 5.5          |
| 55 and over                   | 9.7                      | 2.4          | 0.8          |
| CONDITION ON ADMISSION        |                          |              |              |
| TB -                          | 10.0                     | 19.5         | 20.7         |
| TB + 1                        | 4.6                      | 4.9          | 7.6          |
| TB + 2                        | 35.6                     | 38.7         | 52.2         |
| TB + 3                        | 49.9                     | 36.9         | 19.5         |
| Percentage of male patients.. | 64.9                     | 60.4         | 46.0         |

rising in the later years. This is due in part to the rise in the relative proportion of intermediate cases and in part to the recent employment of pneumoperi-

toneum on a considerable scale. Owing to the increase of waiting lists, patients in recent years have often had longer periods of bed-rest at home or in hospital.

*After history*

The follow-up of patients presented much work and difficulty, particularly on account of the war years. Changes of address were frequent and patients were dispersed throughout the country. Most of Middlesex is the Greater London

TABLE 4  
*Average duration of treatment and number of patients discharged*

| YEAR | DAYS |
|------|------|
| 1937 | 202  |
| 1938 | 207  |
| 1939 | 182  |
| 1940 | 160  |
| 1941 | 185  |
| 1942 | 186  |
| 1943 | 180  |
| 1944 | 202  |
| 1945 | 255  |

TABLE 5  
*Number of patients discharged each year*

| YEAR        | MALE  | FEMALE |
|-------------|-------|--------|
| 1937        | 182   | 101    |
| 1938        | 181   | 98     |
| 1939        | 204   | 108    |
| 1940        | 197   | 129    |
| 1941        | 260   | 158    |
| 1942        | 253   | 178    |
| 1943        | 323   | 342    |
| 1944        | 273   | 327    |
| 1945        | 224   | 295    |
| Total... .. | 2,097 | 1,736  |

urban development and patients are easily lost in the numerous moves which may be undertaken in the metropolitan area. In a small sample of the population (about 8 per cent) it was found that the reason for the removal of half of all names from the local tuberculosis register was because of transfers to other districts. Other effects of war must be remembered in considering the figures presented. The anxieties arising from enemy action and the hardship of war conditions must have played an important part in hindering the recovery of many patients and the maintenance of gain in health. Housing conditions became very difficult.

A follow-up was commenced in 1938. Of the 1,095 males discharged in 1938 to 1942, a total of 79 (7.2 per cent) were lost from observation at the end of three years and the corresponding values for females were 37 (5.5 per cent) of 671 discharges. The number untraced at the end of five years: for discharges during 1938 to 1940, 48 (8.2 per cent) of 582 males; and 29 (8.7 per cent) of 335 females. In the following discussion the "lost from observation" have been dealt with by giving them the average chance of surviving for their age, sex and condition on admission and whether the sputum was positive or negative for tubercle bacilli on discharge. The proportion of patients alive at the end of three and five years following discharge may be seen in table 6. The values in

TABLE 6

*Proportion of patients alive at the end of three and five years following discharge*

| YEAR OF DISCHARGE | PROPORTION SURVIVING THREE YEARS |         | PROPORTION SURVIVING FIVE YEARS |         |
|-------------------|----------------------------------|---------|---------------------------------|---------|
|                   | Males                            | Females | Males                           | Females |
| 1938              | 43.8                             | 60.0    | 41.3                            | 56.9    |
| 1939              | 62.2                             | 55.8    | 52.6                            | 49.2    |
| 1940              | 63.6                             | 64.0    | 55.5                            | 54.9    |
| 1941              | 73.5                             | 77.1    | 62.0                            | 64.5    |
| 1942              | 75.7                             | 79.7    |                                 |         |

TABLE 7

*Percentage standardized survivor ratio three and five years after discharge*

| YEAR | THREE YEARS AFTER DISCHARGE |         | FIVE YEARS AFTER DISCHARGE |         |
|------|-----------------------------|---------|----------------------------|---------|
|      | Males                       | Females | Males                      | Females |
| 1938 | 79.0                        | 104.8   | 84.4                       | 123.2   |
| 1939 | 78.0                        | 80.3    | 96.4                       | 75.4    |
| 1940 | 97.7                        | 92.6    | 103.3                      | 96.9    |
| 1941 | 105.1                       | 104.8   | 108.9                      | 106.9   |
| 1942 | 110.0                       | 110.8   |                            |         |

table 6 reveal that there has been a large increase in the probability of surviving. It has been shown that the constitution of the hospital population varied during the period, for in later years the patients were younger on the average and were less seriously affected on admission. Hence it is difficult to determine from these values whether the increase is real or only apparent. To examine this point, the series of survivors for three years following discharge have been standardized for age and condition on admission and the average of the five years 1938 to 1942 was taken as a standard. The expected number of survivors on this basis was divided into the observed number and the ratio expressed as a percentage. On this basis the mean is 100 and defects and excesses represent a survivorship below and above the average respectively. The results obtained may be seen in table 7. Examination of these values reveals that after allowance has been

made for age and condition on admission there has been a true increase in the percentage surviving three years, the gain being more consistent for males than for females. It is believed that the high values shown in the later years represent a more effective use of collapse therapy, as is further discussed below. It also happened that in 1938 a very high proportion of females underwent collapse treatment. An examination by age gave the results which may be seen in table 8. Young males have a better chance of surviving than young females but at older ages the females have an advantage over the males. This is in accord with the general experience that young men do better than women of similar age.

TABLE 8

*Percentage surviving three years after discharge (1938 to 1942)*

| AGE         | MALES | FEMALES |
|-------------|-------|---------|
| 15 to 24    | 76.6  | 71.5    |
| 25 to 34    | 71.6  | 72.8    |
| 35 and over | 51.6  | 58.1    |

TABLE 9

*Comparison of results from Clare Hall with those from other institutions*

| PERIOD       | EXPERIENCE                         | PERCENTAGE ALIVE<br>AFTER THREE YEARS |         | PERCENTAGE ALIVE<br>AFTER FIVE YEARS |         |
|--------------|------------------------------------|---------------------------------------|---------|--------------------------------------|---------|
|              |                                    | Males                                 | Females | Males                                | Females |
| 1938 to 1942 | Clare Hall                         | 65.2                                  | 69.4    | 53.7                                 | 57.0    |
| 1907 to 1914 | Midhurst                           | 64.8                                  | 66.6    | 53.3                                 | 56.9    |
| 1905 to 1914 | Frimley                            | 66.1                                  | 75.3    | 54.4                                 | 64.8    |
| 1914 to 1916 | Bradford (Vallow)                  | 48.9                                  | 71.7    | 40.8                                 | 63.7    |
| 1928 to 1938 | Durham (Thompson)                  | 35.9                                  |         | 24.7                                 |         |
| 1921 to 1929 | London County Council<br>(Bentley) |                                       |         | 34.2                                 |         |
| 1914 to 1940 | Reading (Tattersall)               | 44.2                                  |         | 32.1                                 |         |

*Comparison with other investigations:* A comparison of the experience of Clare Hall with the results obtained from other inquiries in England may be seen in table 9. The experiences from the various institutions are not strictly comparable, as the proportions in the varying stages of the disease differ among the groups, and the Clare Hall patients have the highest proportion of advanced cases. The Midhurst experience (8) included patients belonging to the professional classes only. The well-to-do and the working industrial classes were not represented. The patients at Frimley (7) were a selected class, as they first passed through a period of observation and treatment at the Brompton Hospital and only those who were likely to derive benefit from a course of sanatorium treatment were sent to Frimley. No such selection of cases was made in Bradford (6) but, while the other investigations were confined to the period following discharge, in this inquiry the chance of surviving three or five years was based on

the date of commencement of treatment. This difference brings the deaths in hospital, which are excluded from the other inquiries, into the calculation of survivorship.

In the Bradford, Frimley, and Midhurst inquiries, the proportion of stage 1 patients approximated 30 per cent and persons with sputum negative for tubercle bacilli were included in this grouping and in the stage 2 and stage 3 cases. It has not been possible to make a comparison with the later Brompton reports (9) or the Midhurst report (10) as the data are presented in a different fashion. The London County Council experience is that of the general sanatorium population. The Durham investigation, while representative of the general population, was based on 406 patients with sputum positive for tubercle bacilli from an area where economic conditions were difficult. These various factors doubtless account for the large differences in the probability of survival. An unknown proportion was treated in sanatoriums but many were too ill, as may be seen from the fact that 42 per cent of the patients died within twelve months of diagnosis. The Reading inquiry was also firmly based on positive cases, some of whom had sanatorium treatment though few had collapse therapy.

The chance of surviving three years or five years after discharge appears much the same in the Clare Hall experience as for Frimley or Midhurst patients except Frimley females, but such a general comparison is of little value without further analysis of the proportions admitted in the various stages. The Clare Hall patients were originally classified into TB -, TB + 1, TB + 2 and TB + 3. The first two categories have been combined in an attempt to make three groups more comparable to the three used in the other investigations although, as noted above, in the Frimley and Midhurst series all groups contain patients who were not expectorating tubercle bacilli. The Clare Hall group 1 patients, therefore, include all minimal or "early" cases, together with a contingent of more advanced but noninfectious cases. Group 2 consists of patients with moderately advanced disease and sputum positive for tubercle bacilli, but who exhibit no marked impairment of function. Group 3 consists of far advanced infectious cases with marked impairment of function, local and constitutional. Allocation was made chiefly on the effect and extent of the pulmonary disease and a prognostic judgment, such as "having little or no prospect of recovery," was not employed. The result of the classification may be seen in table 10.

The males of groups 2 and 3, the more advanced cases discharged from Clare Hall, had a larger proportion surviving three and five years than among those discharged from Frimley and Midhurst. The females did not show such a distinct difference although only one group, survivors after five years in group 3 of Midhurst, had a better experience among the more advanced cases than Clare Hall.

It has already been indicated that selection in favour of the patients admitted to Frimley and to Midhurst is probable. Moreover, the years concerned in the present investigation were overshadowed by war and social conditions and were correspondingly unfavourable. Conversely, weight must be given to the possibility that there may have been some comparative social disadvantages in

1905 to 1914, the period of the Frimley and Midhurst experience, although Drolet (11) and others have put forward evidence to show that the case fatality rate has not improved with the years despite the improvement in the general tuberculosis death rate.

### *Collapse therapy*

Collapse therapy was employed in 1,819 patients, 47.5 per cent of the whole series. The distribution of these patients among the four categories may be

TABLE 10  
*Survival values from four institutions*

|   | MALES*  |         |         | FEMALES* |         |         |
|---|---------|---------|---------|----------|---------|---------|
|   | Group 1 | Group 2 | Group 3 | Group 1  | Group 2 | Group 3 |
| Percentage of survivors three years after discharge |         |         |         |          |         |         |
| Clare Hall.....                                     | 99.8    | 81.4    | 40.4    | 92.5     | 80.5    | 40.0    |
| Midhurst.....                                       | 87.9    | 65.2    | 32.7    | 91.5     | 67.9    | 40.0    |
| Frimley.....  | 91.9    | 69.1    | 35.2    | 99.6     | 80.4    | 34.1    |
| Reading (male and female).....                      | 91.0    | 60.6    | 29.9    |          |         |         |
| Percentage of survivors five years after discharge  |         |         |         |          |         |         |
| Clare Hall.....                                     | 84.9    | 73.6    | 29.3    | 85.8     | 69.7    | 26.0    |
| Midhurst.....                                       | 77.1    | 52.3    | 22.0    | 87.1     | 52.5    | 33.4    |
| Frimley.....  | 87.7    | 56.9    | 21.1    | 94.4     | 67.5    | 21.8    |
| Reading (male and female).....                      | 70.3    | 45.9    | 28.6    |          |         |         |

\* (All sanatorium treated patients.)

TABLE 11  
*Distribution of cases subjected to collapse therapy*

| GROUP  | NUMBER | PER CENT OF GROUP |
|--------|--------|-------------------|
| TB —   | 193    | 26.7              |
| TB ÷ 1 | 112    | 48.0              |
| TB ÷ 2 | 1,107  | 65.2              |
| TB ÷ 3 | 497    | 33.5              |

seen in table 11. As several forms of collapse treatment besides pneumothorax were used in these patients, it is not possible to obtain exactly comparable material from the reports of other English workers. Most of these have dealt solely with pneumothorax, and only in few cases was division of adhesions practiced.

Bentley (5) was mainly concerned in his report with the effects of pneumothorax treatment on prognosis. He analyzed a series of 677 patients who had undergone artificial pneumothorax, among whom approximately 40 per cent had "complete collapse," i.e., a degree of collapse considered satisfactory. The

results were compared with those obtained from 3,329 patients of the same social class discharged in 1927 from sanatorium treatment in the same institutions. The latter patients were "conservatively treated" and did not have collapse therapy. A comparison of these results with those for patients from Clare Hall who had collapse therapy is presented in table 12.

The patients discharged from Clare Hall had a survivorship rate greatly in excess of the London County Council patients who had had artificial pneumothorax. These in turn had a better survival rate than those patients who had only had the more conservative sanatorium treatment. The two series, Clare

TABLE 12

*Comparison of results after collapse therapy (Clare Hall and London County Council)*

|   | PERCENTAGE SURVIVING<br>THREE YEARS<br>AFTER DISCHARGE |         | PERCENTAGE SURVIVING<br>FIVE YEARS<br>AFTER DISCHARGE |         |
|---|--|---------|---|---------|
|   | Males  | Females | Males   | Females |
| Clare Hall (collapse therapy).....                        | 85.1   | 82.4    | 74.6  | 70.5    |
| London County Council (artificial pneumo-<br>thorax)..... | 57.6   | 54.2    | 49.0  | 45.4    |
| London County Council (conservative treat-<br>ment).....  | 37.9   | 41.8    | 28.3  | 31.9    |

TABLE 13

*Stage of disease in Clare Hall and London County Council patients*

| MALES              |            |                       |            | FEMALES            |            |                       |            |
|--------------------|------------|-----------------------|------------|--------------------|------------|-----------------------|------------|
| Clare Hall         |            | London County Council |            | Clare Hall         |            | London County Council |            |
| Stage on admission | Percentage | Stage on admission    | Percentage | Stage on admission | Percentage | Stage on admission    | Percentage |
| TB -               | 9.4        | A                     | 3.9        | TB -               | 15.1       | A                     | 9.3        |
| TB + 1             | 6.0        | B1                    | 4.6        | TB + 1             | 3.6        | B1                    | 1.9        |
| TB + 2             | 51.4       | B2                    | 51.1       | TB + 2             | 56.3       | B2                    | 71.8       |
| TB + 3             | 33.2       | B3                    | 10.4       | TB + 3             | 25.0       | B3                    | 17.0       |

Hall and the London County Council, differ somewhat in composition as regards stage of disease but this is hardly likely to account for the observed differences in survivorship, for the former contained more advanced cases of disease. The proportions in the various stages of the disease may be seen in table 13. The advantage shown by the Clare Hall patients appears to have resulted from the fact that these patients enjoyed more modern resources in collapse therapy, whereas the older London County Council series included those who had artificial pneumothorax which in many cases could not be made into an effective collapse measure, and for whom alternative methods were not then available. This subject is further considered below.

*Sputum conversion ratio:* A useful immediate measure of the success of treatment is obtained by the conversion ratio, found by expressing the percentage of



the infectious cases on admission whose sputum contained no tubercle bacilli on discharge.<sup>3</sup>

The experience of Clare Hall is presented in table 14. As may be seen in table 14, a considerable increase in the proportion discharged with a negative sputum has been effected during the period. As in the previous analyses, a simple comparison is vitiated by the changing constitution of the population as regards age, sex, and condition of disease on admission during the period. To overcome this difficulty, the ratio has been standardized by taking the average for the whole period of those patients admitted with a positive sputum by age, sex, and condition on admission as the standard. The observed number of conversions was expressed as a percentage of the expected; thus ratios over 100 show an improvement on the average while ratios under 100 show a defect. The standardized conversion ratios show that an improvement has been effected during the period

TABLE 14  
*Sputum conversion ratio (Clare Hall patients)*

| YEAR | NUMBER ADMITTED WITH<br>"POSITIVE SPUTUM" | PERCENTAGE CONVERSION<br>RATIO | STANDARDIZED PERCENTAGE CONVERSION<br>RATIO |
|------|---|--------------------------------|---|
| 1937 | 251                                       | 27                             | 69.6  |
| 1938 | 250                                       | 41                             | 109.6                                       |
| 1939 | 236                                       | 35                             | 75.2  |
| 1940 | 275                                       | 39                             | 87.0  |
| 1941 | 333                                       | 53                             | 109.9                                       |
| 1942 | 338                                       | 56                             | 121.1                                       |
| 1943 | 530                                       | 48                             | 88.9  |
| 1944 | 485                                       | 65                             | 106.4                                       |
| 1945 | 399                                       | 69                             | 114.2                                       |

but that annual fluctuations were fairly large. Collapse therapy had been little practiced before the beginning of the period but methods were gradually improved and it seems of interest to compare the trends of the conversion ratios with the proportion of patients undergoing collapse treatment. The standardized ratios for the sum of groups +1, +2, +3 for both variables are shown in figure 1. With the exception of 1938, the trends of the two ratios are similar.

*The intermediate case:* Reference to table 10 reveals that patients in the intermediate group (TB + 2) show special improvement in survival rate when compared with the corresponding groups of earlier sanatorium experience. At Clare Hall particular stress has been given to the fullest possible use of collapse therapy for patients in this group and it is believed that any real improvement in prognosis depends on this. Comparison with the Reading patients who, like those in the present series, were derived from the general dispensary popula-

<sup>3</sup> The criteria of "negative sputum" were as follows: at least three consecutive smears negative for tubercle bacilli or the abolition of all sputum for at least six weeks. In many of such patients, gastric lavage was done and a positive finding barred the patient from the "negative sputum" group.

tion and not from more selected persons, brings out this point clearly. Tattersall (2) notes in regard to his patients, treated in the period 1914 to 1940, that the proportion having collapse therapy was small. The effect of collapse therapy is masked when considering groups TB + 1 and TB + 3. The former contains a large proportion for whom collapse therapy may be considered by some to be unnecessary, while the latter includes many for whom it is impossible. Hence a general survey of the survival of the TB + 2 group of patients, who were followed for five years, provides an opportunity for an evaluation of the effects of collapse therapy. Approximately 69 per cent of the Clare Hall patients in the years under review here were so treated. All patients treated by any measure

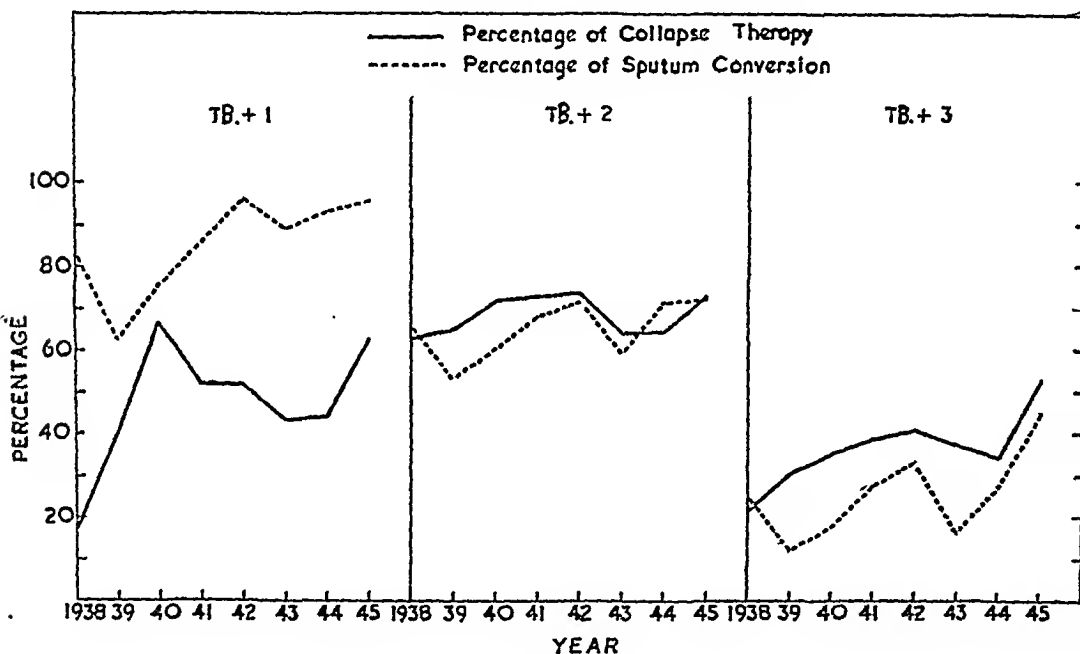


FIG. 1

designed to assist collapse of the lung were included under this heading, with the exception of patients whose pneumothorax could be maintained for less than six weeks and a few who underwent simple phrenic nerve crush only. All others with pneumothorax, phrenic evulsion, thoracoplasty and extrapleural pneumothorax were included. Consequently many whose treatment could not be considered satisfactory are necessarily counted as having "collapse therapy." All patients had careful sanatorium treatment, including bed-rest, for long periods if necessary.

*Comparative value of collapse therapy:* How did patients who had collapse therapy fare in comparison with those in whom such treatment was not applied?

The latter include those in whom pneumothorax space could not be found, or in whom the disease was considered of unsuitable type, or uncooperative patients.

Both classes, it must be remembered, were classified as TB + 2 and hence should otherwise be comparable clinically. There were 442 patients of TB + 2 group followed for at least five years and the results are presented in table 15. As collapse therapy was used in seven out of ten persons, it is clear that its use was not restricted to specially favourable cases, although it was not used in 39 patients who were thought likely to do well without it. It seems fair, therefore, to say that patients in this group treated by collapse measures had a doubled chance of survival as compared with their fellows. Moreover, it is found that those who live for five years after such treatment have a high chance of being fit and able to work, while a greater proportion of invalids is found in the other class.

Even so, comparison of those treated by collapse measures with those for whom such treatment was impossible may be considered as of questionable value. For well-known reasons the latter are very frequently an unsuitable control series. They have perhaps more serious disabilities (*e.g.*, an obliterated pleura), do not have the advantage of constant attendance for review, and are likely to

TABLE 15  
*Comparative value of collapse therapy*

|                                     | PERSONS | SURVIVORS AT FIVE YEARS (PER CENT) |         |     |
|-------------------------------------|---------|------------------------------------|---------|-----|
|                                     |         | Males                              | Females | All |
| Collapse therapy employed.....      | 306     | 81                                 | 77      | 79  |
| Collapse therapy not applied.....   | 97      | 42                                 | 35      | 39  |
| Collapse therapy not attempted..... | 39      |                                    |         |     |
|                                     | 442     |                                    |         |     |

be less cooperative. In the present series these disadvantages are offset to some extent by the high proportion submitted to treatment. Moreover, this large group contained many whose collapse could not be considered satisfactory, but all were included as great difficulties are encountered if selection of only more favourable cases is allowed. It is helpful, however, to compare the collapse therapy treated group with a similar TB + 2 group treated before collapse therapy became more widely used, without pretending that the latter is an exact control group. Thus the 79 per cent survival ratio may be compared with Reading (45.9 per cent) and the more selected Frimley and Midhurst groups (approximately 60 and 52 per cent respectively). In the London County Council series, 306 patients classified as TB + 2 had pneumothorax treatment and 157 (51.3 per cent) survived 5 years. The survival of all patients treated by collapse therapy has already been compared with the survival of the London County Council patients who received sanatorium treatment only (table 12). Edwards (12) reported the information that of patients in the Cheshire Joint Sanatorium treated with pneumothorax and/or phrenic evulsion, 59 per cent were alive five years later, while of those in whom pneumothorax failed and who had no phrenic operation, 47 per cent were alive. It may also be recalled that Braeuning (13) found

that 25 to 48 per cent of cavity bearers were alive after five years, smaller cavities giving more favourable outlook, while Barnes (14) reported that 31 per cent of 122 patients (cavities less than 2 cm. diameter) also lived for that time. Despite the impossibility of providing an exact control group, it is believed that the experience from the present series justifies the view that the prognosis for TB + 2 patients is made nearly twice as good by a full use of collapse therapy and sanatorium treatment. In special groups within this field, especially those for whom efficient pneumothorax and thoracoplasty can be instituted, the chance of surviving is increased above this.

#### DISCUSSION

The notorious difficulty of finding a suitable control group of patients when considering any chronic disease, particularly pulmonary tuberculosis, remains. Hence, even statistical evaluation of the methods of treatment used is not wholly satisfactory, yet repeated attempts are necessary (and permit comparisons) if the possibly still more erroneous deductions from private impressions are to be avoided. The history of the control of tuberculosis is marked by the numerous rejections of treatments advised on high authority but insufficiently supported by weight of evidence. Careful clinical observation, backed by sound statistical inquiry allowing comparison with other work, is the best basis for assessing methods of treatment.

Many or most patients suffering from pulmonary tuberculosis who are brought to treatment undergo improvement at first and hence appear to prove that the particular method used is valuable. Only later results begin to cast doubt on what at first appears so good. Sanatorium treatment of the older type in times when little active interference was undertaken, and the fuller program of the present time with longer periods of bed-rest and much collapse therapy, are both subject to this depression of late results. For this reason, too early assessment is unwise, and even the customary five year follow-up appears to be the minimum period desirable.

The patients considered in the present survey were derived from the general county population with little selection except that patients of obviously bad prognosis in the immediate future would tend to be excluded. Clearly, surveys dating from the beginning of treatment exclude those who die before treatment begins and therefore show favourable bias over surveys of patients dating from notification. In County sanatoriums, however, many patients are admitted whose outlook is known to be poor, but who must be cared for because of lack of facilities at home and to diminish the risk of infection to others.

The importance of ensuring that the groups compared are similar in age and sex distribution is clearly brought out in the present survey. An apparently very favourable improvement in the trend of results is shown to be in part a result of the admission of more favourable subjects for treatment as the years passed. Nevertheless, progress in more efficient bed-rest and collapse therapy, after allowing for the above-mentioned variables, appears to be rewarded by an increase in survival rate (table 7).

In the earlier years facilities at Clare Hall for collapse therapy were limited to the more simple procedures. Hence, pneumothorax treatment was less effective because only a small proportion had adhesion section. The same factor was found in the London County Council series described by Bentley. With adequate surgical assistance it became possible to undertake thoracoscopy for every pneumothorax, and time has shown the wisdom of this policy. Not only are adhesions divided wherever it is possible to do so with safety, but an inefficient and dangerous pneumothorax is less likely to be continued after such inspection. Major surgical procedures could also be more easily undertaken in the later years of the survey.

The present inquiry shows that modern methods of attack on established pulmonary disease have a distinct advantage over the simpler sanatorium treatment of earlier times. This advantage is shown particularly in the TB + 2 group where collapse therapy combined with adequate rest can be most widely employed. It is not possible from the present study to throw any light on the value of simple sanatorium treatment, but such investigations as are available yield no proof of its value as the sole contribution. Stocks and Karn (15) compared sanatorium treated patients and those not so treated and found no essential difference in the chances of surviving. The London County Council patients reviewed by Bentley for the years 1921 to 1929, consisting of all pulmonary patients discharged in each year, showed that 34.2 per cent of these patients were alive five years later. As these patients included TB — patients, it is clear that they attained no definite advantage over other series of "sputum positive" patients which include many untreated persons. Tattersall (2) has also concluded that no proof of the value of simple sanatorium treatment alone could be obtained from his researches in Reading. Analysis of other series of sanatorium treated patients from abroad has led to similar conclusions (4).

It is highly probable that a series of patients subjected to any form of treatment will show improvement when compared with an untreated series for there is an obvious tendency to select patients of more favourable outlook. The same criticisms which apply to the results of "sanatorium" treatment have been applied to series of patients treated by collapse methods. As a true control series is difficult, or even impossible, one must agree with Bentley that comparisons with a large general group are the best resource. In regard to collapse therapy, however, series of treated patients can now be compared with earlier series with a reasonable chance of comparing groups of like character. Bentley's valuable report (5) is particularly helpful for this purpose. Referring to the pneumothorax treated patients he says, "The survival in all the cases investigated was approximately 20 per cent higher in the pneumothorax group than the expected number amongst those conservatively treated. A 20 per cent improvement in 10 per cent of the patients would heighten the general level of results in all cases undergoing residential treatment by 2 per cent. The application of artificial pneumothorax therapy cannot be expected, therefore, to alter materially the gross statistics of the results of anti-tuberculosis schemes, but it will continue to be of vital importance to selected individual sufferers."

Somewhat similar conclusions are derived by Berg (4) from study of Gothenburg patients. He found that for the period 1928 to 1934, the collapse treatment may have slightly influenced the decrease in general mortality for tuberculosis. He says: "A 20 per cent improvement for the treated cases which make up 40 per cent of the cases in this period causes an improvement in mortality amounting to somewhat less than 10 per cent for the total material 1928 to 1934." Both authors, therefore, observe a 20 per cent improvement for patients treated by collapse measures in the relevant periods. In the present study, the figures reveal a further improvement which is believed to be due to more thorough use of the collapse measures now available, supported by adequate bed-rest. If the patients in the intermediate (TB + 2) group only are considered, this advantage is still further increased. The improved results in this group show that the progress noted cannot be due to the inclusion of milder cases among the patients treated by collapse therapy. Improved diagnosis might have made this possible for the total of treated persons, but those patients with the less severe disease would more likely have fallen into the negative or TB + 1 groups.

In these times there is increasing difficulty in admitting patients to sanatoriums and hospitals for tuberculosis, and the most careful use of available resources is therefore important. The aim of those discovering patients suffering from tuberculosis has been to diagnose and treat the "early case." This aim is frustrated, for many patients are discovered with more than slight disease at the first examination. Moreover it is not established that simple sanatorium treatment improves the survival rate of the early case. As there is now increasing evidence of the value of collapse therapy applied according to modern standards, it would appear more logical to use our limited resources as far as possible for the benefit of those who can be treated with real prospect of improvement, namely, those patients with open cavitary tuberculosis who are likely to be amenable to collapse treatment. (It is understood that hospital care for certain advanced cases is essential, and antibiotic or other remedies are indicated for selected patients.) Hence it may be of advantage to treat the patients for whom collapse therapy is unnecessary by a regimen of rest at home, supervised by careful observation at the dispensary. In patients with open cavitary disease the widest possible use should be made of collapse therapy, which should be made as effective as possible, though only continued in its reversible forms where the collapse has been properly established and can be maintained without danger. It is a proper trend for sanatoriums to become more like hospitals in respect of ensuring that adequate surgical and other ancillary facilities are available. The older gains of sanatorium practice, such as the effective use of fresh air and of rehabilitation, have already received wide recognition.

#### SUMMARY

1. There is a tendency to increase the period of treatment of pulmonary tuberculosis in sanatoriums.
2. Improvement in the results of treatment has followed a more active policy of collapse treatment together with careful rest and sanatorium regimen.

3. The results of treatment in the present series appear to show definite improvement over earlier comparable series of patients in England.

4. This improvement is particularly shown in the TB + 2 group, in whom collapse treatment was applied more extensively than in earlier years (approximately 70 per cent). The chance of survival is almost doubled by such treatment.

5. Collapse treatment is the most valuable method at present known for ensuring sputum conversion in "positive" patients, and for their recovery, as estimated by living for five years. Such treatment should be employed as thoroughly as possible, but maintained only when the collapse is made efficient.

#### SUMARIO

##### *Resultados del Tratamiento Sanatorial y de la Colapsoterapia*

1. En los sanatorios reina la tendencia a acrecentar la duración del tratamiento de la tuberculosis pulmonar.

2. Los resultados del tratamiento han mejorado a continuación de una política más activa de colapsoterapia, unida al cuidadoso descanso y régimen sanatorial.

3. Los resultados del tratamiento en la serie aquí descrita parecen revelar una mejora bien definida en comparación con los obtenidos en series anteriores comparables en Inglaterra.

4. Esta mejora se aprecia en particular en el grupo Tb + 2, en el cual se aplicó la colapsoterapia más extensamente que en años anteriores (aproximadamente en 70 por ciento). Las probabilidades de sobrevivencia casi doblaron con dicho tratamiento.

5. La colapsoterapia constituye el método más valioso conocido hoy día para asegurar el viraje del esputo en los enfermos "positivos", y para la reposición de los mismos, calculada en sobrevivencia de cinco años. Dicho tratamiento debe emplearse en la forma más perfecta posible, pero mantenido únicamente cuando el colapso es realmente eficaz.

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## PLEURAL EFFUSION SIMULATING ELEVATED DIAPHRAGM<sup>1,2</sup>

JOHN J. CINCOTTI,<sup>3</sup> STANTON T. ALLISON,<sup>4</sup> AND JOHN M. NILSSON

Atypical distribution of fluid in the pleural cavity offers a challenge to correct diagnosis. In such cases carefully noted physical signs do not correlate with the interpretation of the usual roentgenograms. The writers have recently observed a case in which intrapleural effusion simulated a greatly elevated diaphragm. This case is reported and the literature reviewed. It is our purpose to re-emphasize the occurrence of these unusually distributed effusions and to add certain diagnostic criteria.

### CASE REPORT

A 25-year-old white soldier was admitted to an Army General Hospital in January 1945, following a severe pulmonary hemorrhage. Chest examination and roentgenograms at that time revealed right apical pulmonary disease with cavity formation. The sputum contained acid-fast bacilli. The hemoptysis subsided spontaneously and, after a period of bed-rest and observation, the patient was transferred to the Veterans Administration Hospital, Rutland Heights, Massachusetts, on September 8, 1945. Right therapeutic artificial pneumothorax was instituted on September 21, 1945. An excellent collapse was obtained and the sputum was negative for tubercle bacilli in March 1946. In February 1947, after four months of graduated exercises, he returned from a ten day hospital leave acutely ill with fever, cough, and weakness. A chest roentgenogram now revealed a pneumonic process involving the apex of the left lower lobe with an area of central rarefaction suggesting cavity formation. The sputum was positive for tubercle bacilli.

On February 21, 1947, the intramuscular administration of streptomycin hydrochloride, 2.0 gm. daily in divided doses, was begun. Because of continued toxicity and lack of roentgenographic evidence of clearing, the dose was subsequently increased to 3.0 gm. daily. On March third erythema and urticaria of the face, arms, and legs, and slight swelling of the knees and knuckles, was observed. This was unrelieved by Benadryl and Pyribenzamine, and streptomycin was temporarily discontinued. A desensitization course of streptomycin was started March 19th without the reappearance of these lesions. Consequently, the patient was again started on 2.0 gm. streptomycin daily. On May 5th a two months course of streptomycin was completed. The patient had improved symptomatically and had gained 11 pounds. The sputum became negative for tubercle

<sup>1</sup> From Veterans Administration Hospital, Rutland Heights, Massachusetts.

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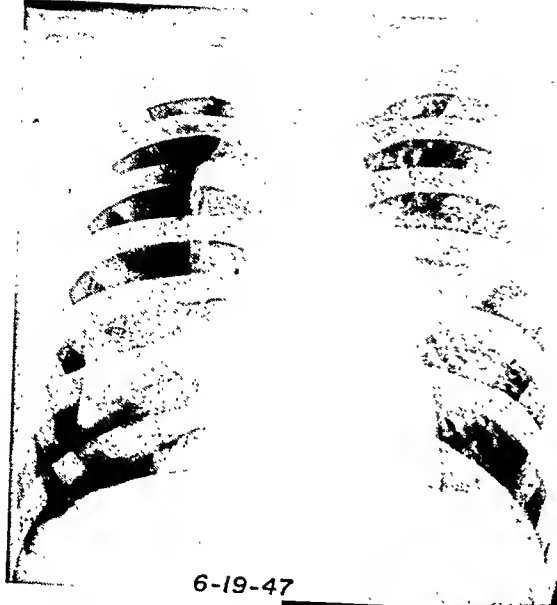
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FIG. 1. (Upper left). Chest film, June 1947, revealing no evidence of intrapleural fluid.

FIG. 2. (Upper right). Later film, July 1947, revealed fluid in *right* costophrenic angle at time of onset of *left* pleural pain.

FIG. 3. (Centre). Film, August 1947, interpreted as showing slight elevation of left diaphragm.

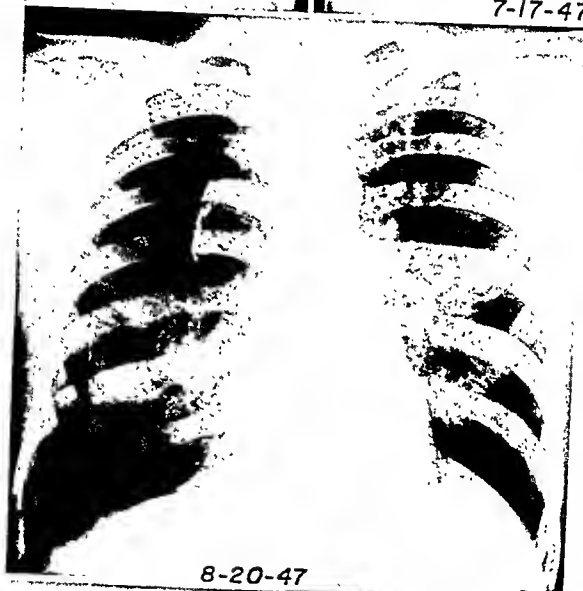
FIGS. 4 and 5 (Lower left and right). Later film of August 1947 revealing apparent further elevation of left diaphragm.



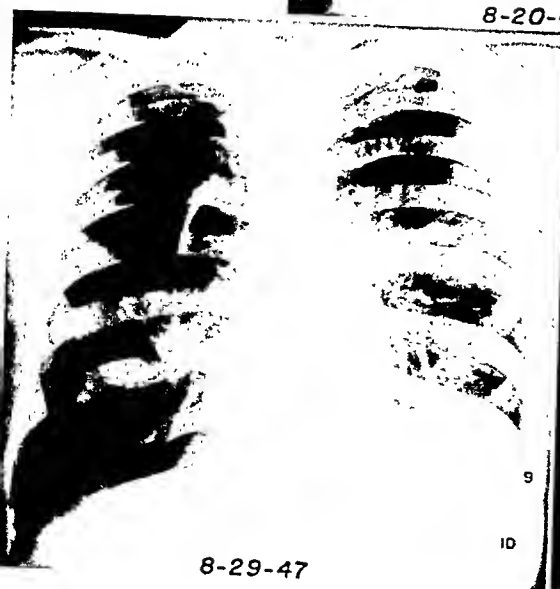
6-19-47



7-17-47



8-20-47



8-29-47


9

10




8-29-47


FIGS. 1-5




9-2-47



9-2-47



9-2-47



9-2-47  
AFTER THORACENTESIS  
OF 1400cc

bacilli on seventy-two hour concentration on April 29, 1947, and chest roentgenograms showed marked clearing with no evidence of cavitation.

During the month of June 1947, the patient complained of intermittent chest pain on his pneumothorax side. Weekly fluoroscopy, however, revealed no evidence of fluid (figure 1). In the middle of July 1947 (figure 2), he first experienced fleeting pain in the left chest. The pain was confined to the left lower anterior aspect of the chest and was intensified by deep breathing. Temperature, pulse, and respiration were normal and the physical examination of the left chest was negative. Examination of the right chest (with pneumothorax), however, now disclosed minimal obliteration of the costophrenic angle by fluid. The patient was asymptomatic until August 16, 1947, when he complained of sore throat. His temperature at this time was 99°F. His pharynx was moderately inflamed and the cervical lymph nodes were palpable bilaterally. Fluoroscopic study at this time revealed what appeared to be a slightly elevated left diaphragm which exhibited normal excursion. On the right side a 60 per cent pneumothorax and a clear smooth diaphragm were present. Inconstant left chest pain recurred during this episode but disappeared quickly.

Abnormal physical signs were first noted on examination on August 20, 1947, when the left chest showed slight impairment of resonance posterolaterally. The breath sounds and voice sounds, however, were essentially normal (figure 3). There was no friction rub. The temperature was 101°F. The diaphragm had apparently risen three fingers' breadth by August 29, (figures 4 and 5). Bronchoscopic examination at this time revealed no cause for the elevation of the left diaphragm. By September 2nd the left chest pain had become more acute and the temperature had risen to 102°F. The percussion note was dull at the left base and auscultation brought out diminished breath sounds and a friction rub.

A postero-anterior inspiratory film revealed shadows interpreted as representing a highly elevated left diaphragm with a clear costophrenic angle (figure 6). This interpretation was corroborated by fluoroscopy which disclosed in addition that the apparent diaphragmatic contour moved in a normal direction. A postero-anterior erect film taken in forced expiration, however, revealed a change in the apparent diaphragmatic contour from convex to the typical S-line of intrapleural effusion (figure 7). A repeat inspiratory roentgenogram demonstrated the return of the original atypical convexity. The patient then was given an effervescent mixture (Seidlitz powder) orally and was re-examined under fluoroscopy. A large gastric air bubble was noted below a normally situated diaphragm and the convex contour of atypical effusion was seen 3.5 inches above at the level of the ninth rib posteriorly (figure 8). Thoracentesis was performed in the sixth intercostal space at the anterior axillary line with the recovery of 1,400 cc. of clear amber fluid. The patient's temperature quickly returned to normal and his symptoms abated (figure 9). The specific gravity of the fluid was 1.016 and the cell count was 200 per cu. mm., most of which were lymphocytes. Smear and guinea pig inoculation of the fluid failed to reveal tubercle bacilli.

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FIGS. 6 and 7 (Upper left and right). Chest films obtained in inspiration and expiration on September 2, 1947. Note change from convex contours (figure 6) to the typical S-line of intrapleural effusion (figure 7).

FIG. 8 (Lower left). Film obtained after ingestion of Seidlitz powder. Note gastric air bubble beneath normally situated diaphragm and shadow of effusion above.

FIG. 9 (Lower right). Chest film, taken same day as figures 6, 7 and 8 after removal of 1400 cc. fluid from pleural cavity.

## COMMENT

An atypical distribution of pleural effusion may be defined as a subtotal intrapleural collection of fluid, transudate or exudate, which in the erect inspiratory postero-anterior film does not conform to the S-line of Ellis or Damoiseau. That the S-line configuration does not always appear in simple subtotal effusion has been described by Rigler (1, 2), Yater and Rodis (4), and recently by Parsonnet (5). Rigler (3), in his classification of the roentgenographic appearance of atypical effusion, described four groups: (a) The most common is a variation in the degree of concavity of the fluid level, the almost flat effusion, which simulates hydropneumothorax. (b) The next in frequency is the somewhat convex type which gives the appearance of elevated diaphragm. (c) The third group shows fluid chiefly in the mediastinal pleural space. (d) The fourth group consists of interlobar effusions.

The physical factors concerned in the roentgenographic appearance presented by any pleural effusion appear to be the force of gravity, as distorted in an airless pleural space by parenchymal retractility; capillarity (cohesion); and adhesions of the pleurae, and fluid surface tension (3, 5). Which variant, or combination, is responsible for these atypically distributed effusions is still conjectural. The fluid is usually a transudate. Rigler's group (b), which simulates an elevated diaphragm, has been seen by him in some six instances. Yater and Rodis (4) reported an exceptionally illustrative case which simulated a greatly elevated diaphragm. Parsonnet, Klosk, and Bernstein (5) recently described three additional cases.

Roentgenographically these cases are characterized by a convex diaphragm-like contour which varies in degree of convexity, smoothness and elevation. The fluid is not necessarily encapsulated, for autopsy in one of Parsonnet's cases revealed a pleural cavity which was devoid of adhesions. Yater and Rodis' postmortem study revealed that the fluid was partially encapsulated above the diaphragm by fibrinous adhesions, but escaped rather freely into the general pleural cavity. Rigler stated that the fluid is nonencapsulated in transudates and early exudates.

Rigler (3) has stressed the importance of a prone or supine position film which shows the fluid distributed over the central lung field. Frequently such a film will reveal a clear, normally placed diaphragm some distance caudad to the free fluid density. He also advises taking a lateral decubitus film which reveals the fluid quite flat in the inferior costal gutter and the diaphragm clearly outlined in a normal position. Encapsulation occurs in viscid exudates with early adhesion formation and also may occur in late transudates. Pneumoperitoneum was utilized as a diagnostic aid by Parsonnet and his associates. The procedure is recommended in cases where encapsulation is a factor. These investigators observed that the convex contour of the fluid changed to the usual S-line of intrapleural fluid after the induction of pneumoperitoneum. In the case of the present report the same type of change was demonstrated by the simple expedient of taking an erect chest roentgenogram in forced expiration. This can be demon-

strated by fluoroscopy. During voluntary forced elevation of a diaphragm the fluid is forcibly displaced into the peripheral pleural space and gives the familiar S-line of intrapleural effusion. Immediately following forced expiration the fluid assumes its original convex contour. Yater and Rodis noticed that the central lung field density, seen on supine fluoroscopy, did not materially change as the patient became erect until the last moment, when suddenly the original convex appearance returned. They noted that on erect fluoroscopy the contour transmitted the cardiac impulse. Miller (6) stated that the contour moves in a more or less normal excursion. The writers have confirmed this observation.

When this uncommon distribution of pleural fluid occurs, the diagnosis may be difficult. The physical findings may be equivocal or may be those of fluid. If those of fluid, the signs are essentially the same whether the fluid is above or below the diaphragm (5, 6).

The seemingly high diaphragm-like contour may be erroneously attributed to: the elevated diaphragm of acute dry pleurisy; the anteromedial bulge or partial eventration of Eisler (8, 9), which appears in exaggerated form in the presence of intrapulmonary lesions (11); eventration of the diaphragm; lesions producing phrenic paralysis; pseudo-adhesion of Matson (14); or to the peculiar saucer-deformity type of pseudo-adhesion reported by Middleton (15). The condition must be distinguished from the "formes frustes" of perforated peptic ulcer without pneumoperitoneum (9, 10); the Morgagni type of diaphragmatic hernia; pericardiophrenic cysts (16); atelectasis; pleural adhesion and gastric distention; the transient elevations of both or either diaphragm following surgery, which may persist for several weeks (17); hepatomegaly and, rarely, splenomegaly; and perinephritic or subphrenic abscess. Parsonnet's three cases occurred in cardiacs with chronic congestive failure (5). Rigler (3) observed atypical effusion in 3 patients with lipoid nephrosis, one of whom fell into his group ((b) simulated elevated diaphragm). He noted that these fluids contain an excess of lipoid substance which lowers surface tension.

#### SUMMARY

The collected cases of pleural effusion simulating elevated diaphragm demonstrate the apparent rarity of this condition. The difficulties encountered in proving the diagnosis may account for the paucity of reported cases. Many cases are probably overlooked when the diaphragm is but slightly elevated or erroneously considered to represent a slightly elevated diaphragm. Efforts must be directed to the proper evaluation of all elevated diaphragms. Rigler's techniques and classification have not been adequately stressed and are of great assistance in the diagnosis of transudates and early exudates which are atypical in their roentgenographic distribution. Moreover, in effusions simulating elevated diaphragm, expiratory film studies may be of considerable value. In encapsulated transudates and exudates, Parsonnet's suggested pneumoperitoneum is to be strongly recommended, especially if the gastric gas bubble contrast is not conclusive. The

usefulness of the latter technique is limited by the fact that it is only applicable in effusions of the left side.

# SUMARIO

## *Derrame Pleural Simulando Elevación del Diafragma*

Una compilación de casos de derrame pleural simulando elevación del diafragma revela la aparente rareza del estado. Las dificultades encontradas al tratar de comprobar el diagnóstico tal vez expliquen la escasez de los casos comunicados. Muchos se pasan probablemente por alto si el diafragma sólo se halla ligeramente elevado o se considera erróneamente en ellos que representan una leve elevación. Hay que esforzarse por justipreciar debidamente toda elevación diafragmática. Las técnicas y clasificación de Riggler no han sido adecuadamente recalculadas, aunque son de mucha ayuda en el diagnóstico de los trasudados y los exudados recientes de atípica distribución roentgenográfica. Además, en los derrames que simulan elevación del diafragma, los estudios de las radiografías tomadas durante la espiración pueden poseer valor considerable. En los trasudados y exudados encapsulados, cabe recomendar con vigor el neumoperitoneo propuesto por Personnet, máxime si el contraste con la burbuja gástrica de gas no resulta terminante. La utilidad de esta última técnica adolece de la limitación de que sólo tiene aplicación en los derrames del lado izquierdo.

# Acknowledgment

The writers wish to express gratitude for the aid given by our consultants, Dr. L. F. Davenport (Medicine) and Dr. D. E. Harken (Thoracic Surgery) and by Dr. S. S. Hoechstetter, radiologist, Veterans Administration Hospital, Rutland Heights, Massachusetts

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## HISTOPLASMOSIS<sup>1</sup>

WILLIAM B. DUBLIN, CLYDE G. CULBERTSON AND  
HERBERT P. FRIEDMAN

A case of generalized histoplasmosis in which the diagnosis was made by biopsy of a lymph node, and in which the histoplasmin test was repeatedly negative, is the subject of this report.

### CASE REPORT

The patient, B. J. S., a white single woman aged 21, having no complaint, was subjected by her employer to routine (survey) roentgenologic study of the chest. A pulmonary lesion was found and on August 3, 1946, the patient was directed to consult her physician. She admitted only that she had lost five pounds during the preceding month. Physical examination showed diminution of breath sounds, dullness, and medium and fine rales in the right lower pulmonary region. A roentgenogram of the chest (figure 1) revealed infiltration in each lung, especially on the right, where, inferiorly, there appeared an area, 5 cm. in diameter, of conglomerate nodules. The hilar nodes appeared greatly enlarged. No cervical lymph nodes could be felt.

The patient felt so well that she refused hospital care but she rested in bed for one month. During this time, no elevation of temperature was observed and ten daily examinations of sputum for acid-fast bacilli yielded negative results. There were still no symptoms. Determinations of hemoglobin, erythrocytes and leucocytes were within normal limits. Bluish, erythematous, roughened cutaneous areas appeared over the knees. Inspection and biopsy of these lesions yielded an impression of seborrheic dermatitis, and there was no evidence of granuloma. On September 5, 1946, a roentgenogram showed definite bilateral progression of the lesions.

The patient was admitted to St. Vincent's Hospital. Hematologic values remained within normal limits and there were still no symptoms. Bronchoscopic lavage yielded negative results in spite of pointed search for *Histoplasma* along with other suspected agents. An intracutaneous test with Old Tuberculin, 1:1,000, yielded a two plus reaction. A similar test with a fresh 1:1,000 preparation of histoplasmin, obtained from the laboratories of the United States Public Health Service at the University of Kansas, produced no reaction.

The patient's father had died fifteen years previously in Sunnyside Sanatorium. At autopsy, a diagnosis had been made of tuberculosis. Histologic study had not been extensive and sections are not available for review. Because of the foregoing family background and economic circumstances, the patient was accepted, undiagnosed, at Sunnyside Sanatorium. At this time, the patient first experienced a feeling of mild general illness. On examination in the sanatorium, pulmonary infiltrations were again found in the roentgenogram of the chest. Repeated examination of sputum for acid-fast bacilli was negative, as was inoculation of a guinea pig. The patient lost weight and became increasingly ill. On January 1, 1947, small firm cervical lymph nodes appeared. One of these was removed for biopsy. Histologic examination by one of the writers (W. B. D.) revealed a fibrocaseous granulomatous process in which there appeared numerous large macrophages containing typical *Histoplasma* capsulatum.

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The patient was transferred, January 1, 1947, to Indianapolis General Hospital. Physical examination showed a systolic blood pressure of 98 mm. of Hg. and a diastolic pressure of 46 mm. Hg. The average daily temperature was 100° F. by mouth. The pulse was 134 per minute, and the respirations, 20. The patient was quite emaciated. She coughed intermittently. There were small, firm cervical and axillary lymph nodes. There was evidence of massive involvement of the right lower lung field, with decreased vocal fremitus and dullness to percussion as well as diminution of breath sounds. Fine and moderately fine moist rales were heard on the left side of the chest from the sixth rib, inferiorly. The liver and spleen were palpably enlarged. Of particular interest was a leucocytosis, varying from 15,000 to 30,000 leucocytes per cu. mm., most of the cells being neutrophils. Lymphocytes, monocytes, and neutrophils showed no organisms on a blood smear prepared with Wright's stain. Buffy coat smears were also negative. The

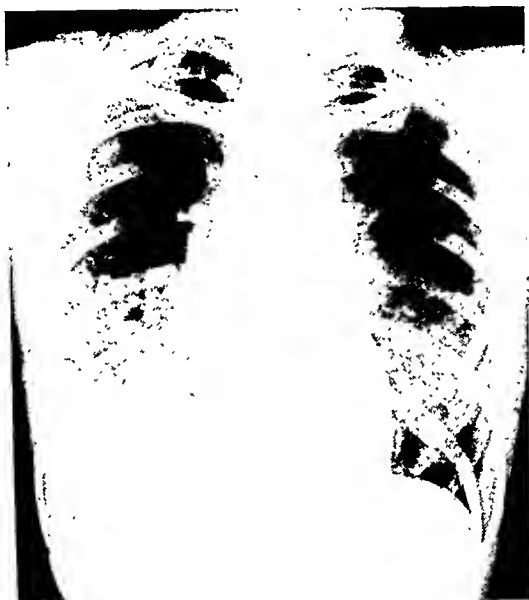


FIG. 1. Roentgenogram of chest, August 3, 1946

concentration of hemoglobin was 10 gm. per cent and the total erythrocyte count was 3.5 million per cu. mm. On January 22, 1947, roentgenologic examination of the chest (figure 2) revealed complete loss of detail in the right lower lung field and the other infiltrations were increased over the extent shown in earlier films. The patient was treated supportively with blood transfusions but became progressively weaker and died February 8, 1947.

A skin test made by one of the writers (C. G. C.) with 1:1,000 dilution of histoplasmin Lilly was repeatedly negative. The material consisted of 1:1,000 dilution of a filtrate of the growth. (The lot of filtrate used in this case had been giving satisfactory positive results using the dilution mentioned and did not give positive reactions in a number of cases where it was used undiluted.) The test was not repeated with stronger dilutions. Complement fixation tests, using a heat-killed antigen of the mold form of the organism and also concentrated histoplasmin filtrate, were negative. Both antigens had been injected into rabbits and positive results with complement fixation had been obtained with the rabbit serum which showed only a slight tendency to cross fixation. Antiserum

produced by intravenous injection of the concentrated filtrate gave a four plus reaction in a 1:40 dilution of the serum when the homologous filtrate antigen was used and only three plus in 1:10 when tests were conducted with the ground mycelial antigen. The reverse was true to a slight extent, for antiserum produced by injecting mycelial antigen gave four plus reactions in 1:10 dilution with the homologous mycelial antigen and two plus in 1:10 dilution with the filtrate antigen. With antigens thus tested, the serum of this patient was twice entirely negative when in the same test the rabbit sera showed results similar to those described previously. These negative findings are similar to the findings of other workers (1).

Histologic interpretation of the aforementioned lymph node was supported by recovery of *Histoplasma* from specimens of blood and pleural fluid. Citrated blood was treated according to previous experience with a child's blood by one of the writers (C. G. C.) in 1939. In the former case, 5 cc. of blood drawn into a sterile syringe containing 1 cc. sterile 2.5 per cent sodium citrate was allowed to stand at room tempera-

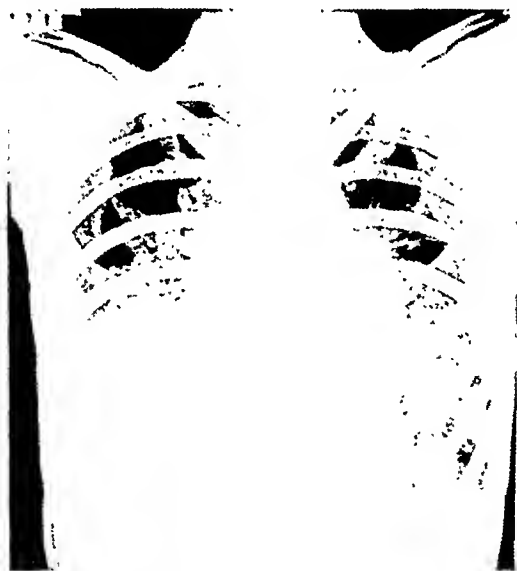


FIG. 2. Roentgenogram of chest, January 22, 1947

ture. After about two weeks, a white mycelial growth, identified as *Histoplasma capsulatum*, appeared just above the leucocyte platelet layer.

In the present case, similar results were obtained. A blood specimen, drawn in the manner described previously, was allowed to stand in the dark for two weeks at room temperature. In figure 3 may be seen the small colonies making their appearance, and in figure 4 the growth some ten days later.

Specimens of pleural fluid, placed on Sabouraud's medium at room temperature and at 37° C., yielded the organism (figure 5).

In all cultures, typical tuberculate chlamydo-spores were identified (figure 6). The diagnosis was kindly confirmed by Doctor Norman F. Conant, Duke University School of Medicine.

Postmortem examination was performed seven hours after death, the body having been embalmed three hours after death. Only the important findings will be described, briefly.

Areas of reddish roughening suggesting an exfoliative dermatitis were present over the trunk and lower limbs anteriorly. Emaciation was marked. Turbid, straw-colored fluid was abundant in the pleural, pericardial, and abdominal cavities.

The mediastinum was extensively infiltrated by firm, yellow to white, fibrous to caseous, granuloma. Similar infiltration was present massively, both in solid and in nodular distribution, in regions producing shadows in the pulmonary roentgenogram (figure 7).

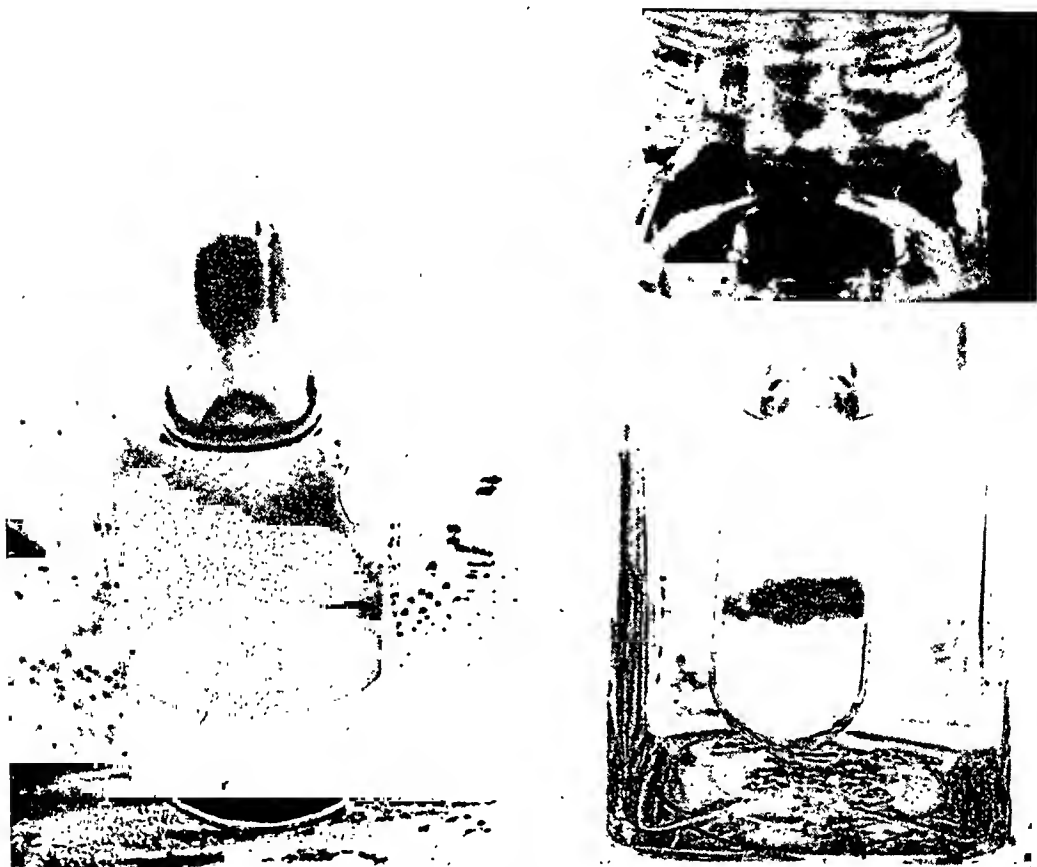


FIG. 3. (Left) Early growth from buffy layer of citrated whole blood kept at room temperature in the dark for two weeks.

FIG. 4. (Right) The same, two weeks later.

The liver weighed 1,750 grams and the spleen, 850 grams. Both contained scattered, firm, necrotic areas (figure 8). The third lumbar vertebral body contained an area, 1 cm. in diameter, of firm, white, granulomatous tissue (figure 9).

All other viscera, including the entire nervous, gastro-intestinal, and genito-urinary systems, breasts, thyroid, major blood vessels, and adrenals were within normal limits grossly, except for grade II cerebral edema.

Microscopic examination revealed a fibrocaseous, granulomatous process (figure 10) containing occasional tuberculoid features and numerous macrophages containing typical *Histoplasma capsulatum* (figure 11). The lesions appeared massively in lungs, liver, spleen, lymph nodes, thymus, and vertebra, and infrequently in pericardium, kidneys,

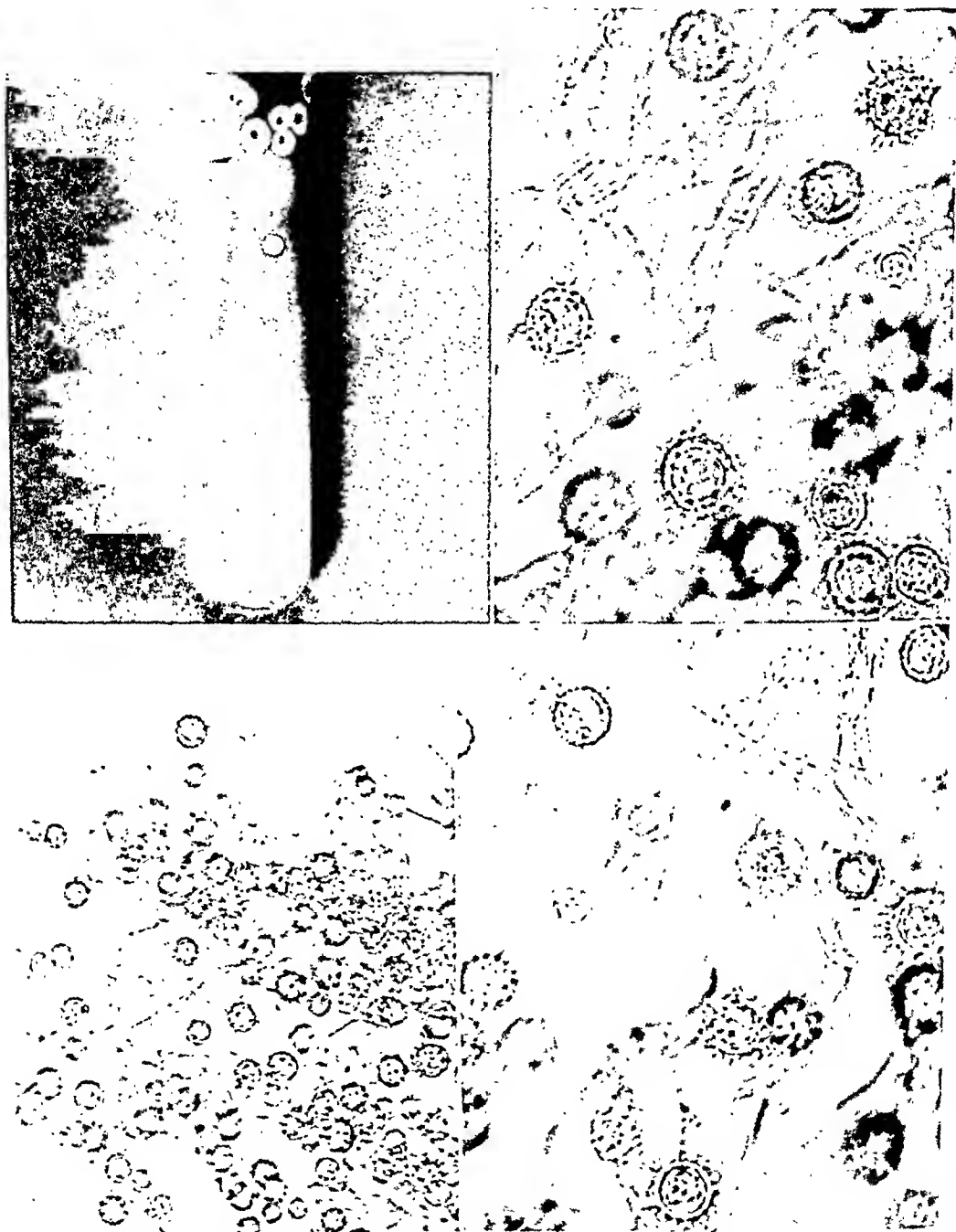


FIG. 5. (Upper left) Growth from pleural fluid on Sabouraud's medium at room temperature in subdued light, after two weeks.

FIGS. 6a, 6b and 6c. (Upper right, lower left and right) Tuberculate chlamydospores and filaments from culture shown in figure 5.

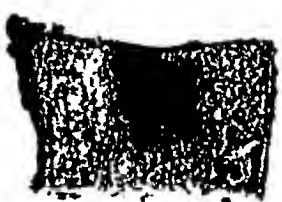
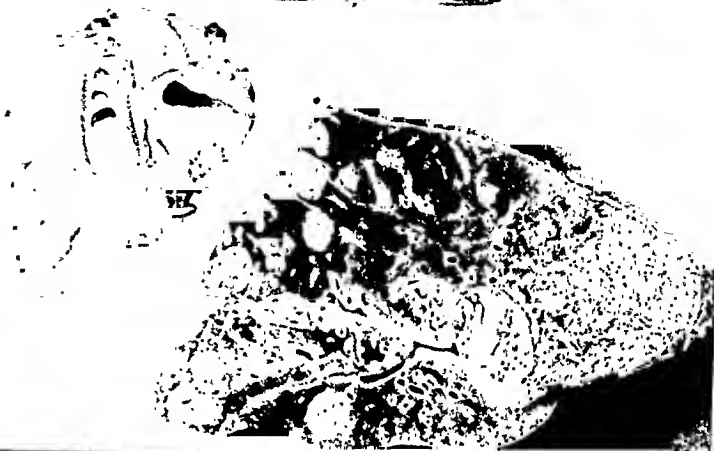
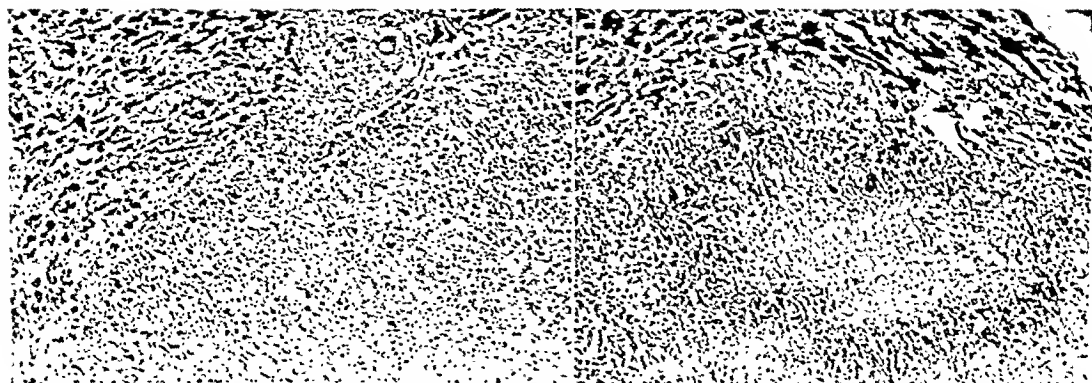


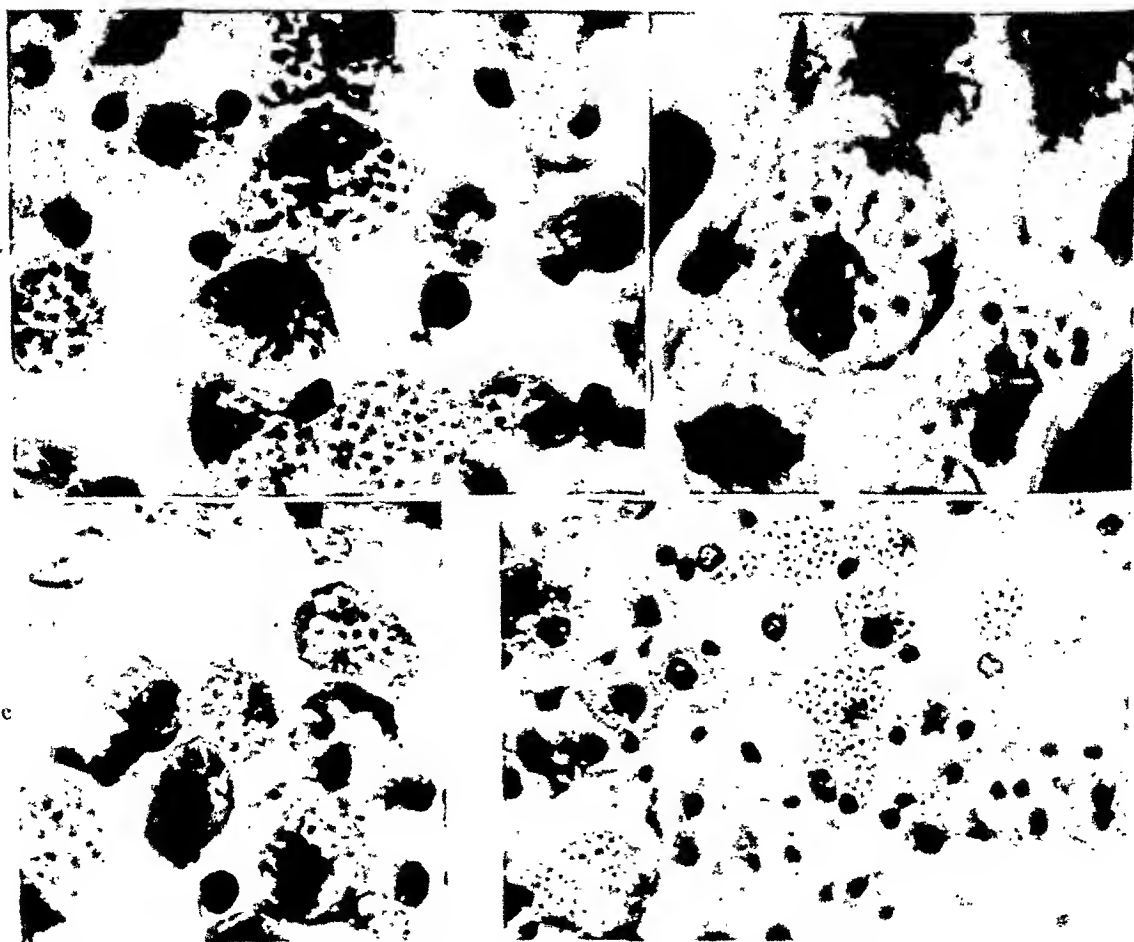
Fig. 7. (Upper left) Lungs, the right lower lobe showing solid involvement and the tracheobronchial lymph nodes being involved by the granuloma.

Fig. 8. (Upper right) Liver and spleen, showing involvement.

Fig. 9. (Lower left) Third lumbar vertebral body, area of involvement.



FIGS. 10a and 10b. Microscopic sections of liver, showing fibrocascous granuloma.



FIGS. 11a, 11b, 11c and 11d. Microscopic sections of lung, showing macrophages containing *Histo-plasma capsulatum*.

adrenals, intestinal mucosa, and bladder. Rare organisms were found in virtually every organ studied. No *Histoplasma* were found in the intrinsic tissues of the nervous system, however. The few which were seen were situated, mainly within macrophages, within or without vessels, in the meninges.

#### DISCUSSION

This patient, as have most of those studied previously, gave negative results to tests with histoplasmin. The concept expressed by Christie and Peterson (2) of the similarity of histoplasmosis to coccidioidomycosis seems a logical one. The probable similarity of the test to the tuberculin test also is obvious, as almost all disseminated fatal cases give negative tests. Sensitivity to intradermal injections of histoplasmin in proper dosage has been shown by several investigators, particularly Christie and Peterson, to indicate initial infections with the fungus which generally heal. These lesions may result in pulmonary calcification. The possibility of cross reaction with other fungi has been cited by Emmons (3), but later when dosage was reduced the cross reactions in experimental animals were not extensive (4). It appears that too concentrated histoplasmin filtrates may therefore give erroneous reactions in the human. In the opinion of the writers this question will be answered only by further painstaking autopsy studies made, in children succumbing to other diseases, to correlate small foci of histoplasmosis in the lungs with positive histoplasmin tests.

On the basis of the present knowledge concerning histoplasmin skin tests, it seems that it is of greatest value in epidemiological studies in connection with the "primary" or sensitizing infections. If an individual is suspected of having late disseminated histoplasmosis, it is to be remembered that the histoplasmin may be negative. It is also to be remembered that strong filtrates are irritating in themselves and will give reactions in nonsensitized animals, so that the use of filtrates which give an excessive per cent of positive tests in a given community is not recommended. The writers have seen one such lot which caused sloughs in sensitive individuals at a dilution of 1:1,000. An antigen which gives definite induration in a known sensitive individual in forty-eight hours in a dilution of 1:1,000 seems much more desirable. The antigen (S200C) used on this patient was erroneously injected undiluted into a number of children and several perfectly negative tests resulted although the positive tests were extremely severe. No set methods of standardization are available.

#### SUMMARY

1. A case of generalized histoplasmosis is reported in which the diagnosis was made by biopsy of a cervical lymph node.
2. The organism grew from the huffy layer of the blood after 5.0 cc. of citrated blood were allowed to stand for two weeks at room temperature.
3. Complement fixation tests using ground mycelial and also filtrate antigens were negative. (Since the tests were made on this patient, positive results of complement fixation tests have been reported in similar cases (5, 6, 7).)
4. The significance of histoplasmin tests is discussed.



## SUMARIO

*Histoplasmosis*

1. En el caso de histoplasmosis generalizada aquí descrito el diagnóstico se basó en la biopsia de un ganglio linfático cervical.

2. El microbio proliferó en la capa anticada de la sangre después de dejar reposar 5.0 cc. de sangre citratada durante dos semanas a la temperatura ambiente.

3. Las reacciones de fijación del complemento, usando antígenos miceliales triturados, y también filtrados, resultaron negativas. (Después de hacer las pruebas en este enfermo, se han comunicado reacciones positivas de fijación del complemento en casos semejantes [5, 6, 7]).

4. Discútese la significación de las pruebas de la histoplasmina.

*Acknowledgment*

The authors wish to express their thanks to Dr. Frank Jennings, Superintendent, Sunnyside Sanatorium, Dr. Russell S. Henry and Dr. David F. Stone for clinical data; and to Doctor Henry, and to Dr. Lester A. Smith, Radiologist, Indianapolis General Hospital, for permission to reproduce the roentgenograms.

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# THE PRESERVATION OF THE BCG STRAIN

F. VAN DEINSE

The interest in BCG vaccination existing today in the United States and in other countries has stimulated the writer to describe in some detail the technique of conservation of the BCG strain, as it is applied in the Pasteur Institute, where BCG was first cultivated by Calmette and Guérin and where the best way of preserving its vitality and its vaccinating properties has been described by these authors.

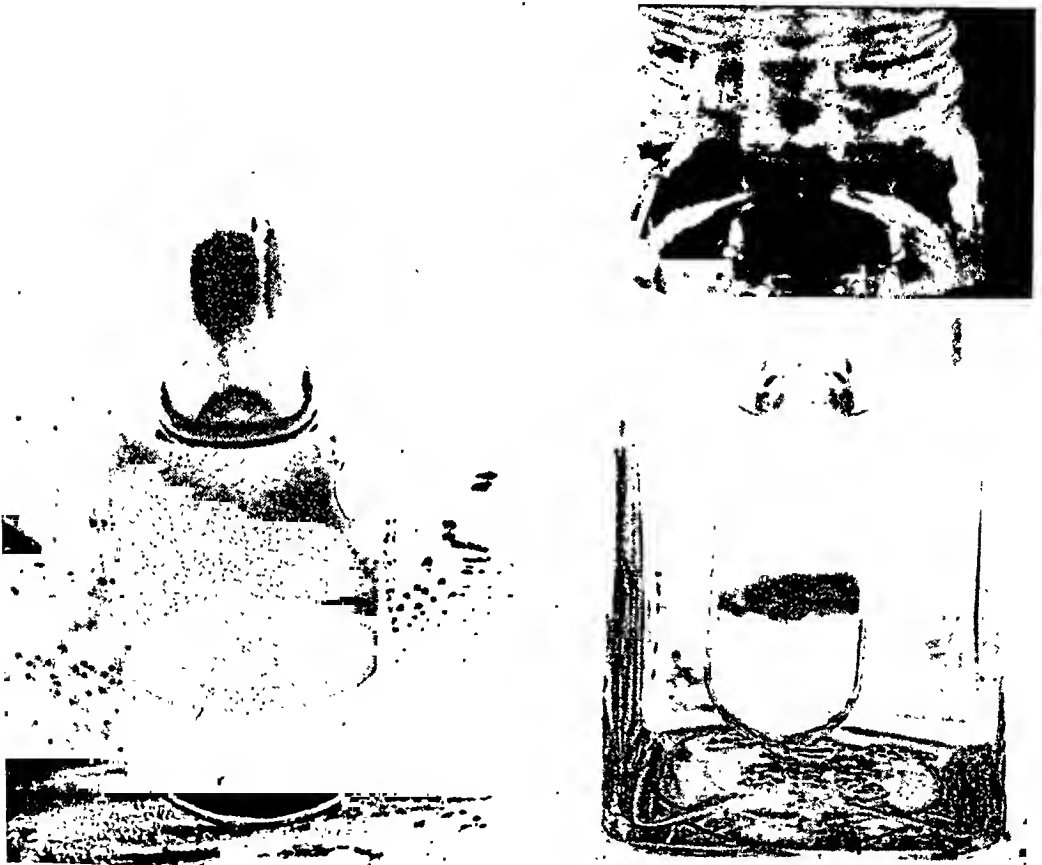


FIG. 3. (Left) Early growth from buffy layer of citrated whole blood kept at room temperature in the dark for two weeks.

FIG. 4. (Right) The same, two weeks later.

Experience at the Pasteur Institute with BCG vaccination covers a period of twenty-five years, and no complaints have ever been received concerning a loss of the immunizing or of the allergizing power of the BCG strain. It has become routine in this department to inoculate guinea pigs intradermally with minute doses of BCG to determine the presence of the slight virulence of the strain, without which its antigenic properties would be abolished. A fourteen day old culture on Sauton-potato of this BCG strain injected intradermally in guinea pigs in a dose of 0.01 mg. (suspended in 0.1 cc. saline solution) produces a small red nodule, about 3 mm. in diameter, within one or two weeks according to the individual sensitivity of the animal. The nodule disappears after eight to fifteen days.

In 1946, K. A. Jensen of Copenhagen published an article (1) in which he gave a very complete description of what he considers as variations of the virulence of two BCG strains, received from Calmette in 1927 and 1931, respectively. The first strain (1927) proved to be too virulent for intradermal or subcutaneous injection in man, as it too frequently caused local abscesses and ulcerations. The second strain (423, 1931) was found to be less virulent and was more suitable for human use. As in that period BCG vaccination was carried out in France by the oral way exclusively, such differences in virulence had not been noted. As Jensen points out, it is impossible to elucidate such slight differences of virulence by massive injection (5.0 mg.) in guinea pigs as both strains (1927 and 1931) were equally nonpathogenic when tested in this way. Intradermal inoculations of very small doses in the guinea pig are necessary in order to detect such differences experimentally.

A striking fact in Jensen's investigations is the fact that he observed an increase of virulence in the 1931 strain when kept continually on bile potato through a series of passages. As he points out, this is in conflict with the statement made by Calmette. Indeed, the virulent bovine strain of tubercle bacilli, isolated in 1902 by Nocard at the Veterinary School at Alfort and used by Calmette and Guérin in their experiments on oral infections of calves, rapidly lost its virulence when cultured on the bile potato medium. These investigators used this medium because they found it to be a convenient way of obtaining homogenous suspensions of their culture in saline solution. This observed loss of virulence gave them the idea of exploiting the technique of subculturing the strain on bile potato for a long period. Transfers on this unusual medium were made every two weeks for a period of thirteen years in order to obtain a living, nonvirulent strain of tubercle bacilli suitable for vaccination. Thus, the birth of BCG was the result of a fortuitous observation. It seems paradoxical that there would be a renewal of real virulence in BCG when cultivated on the exact medium on which it originally lost its virulence.

Another striking fact in Jensen's report is the observation that certain periods during which the virulence of the BCG vaccine was reduced, as tested intradermally in guinea pigs, coincided with complaints from vaccinating pediatricians that the vaccinated children failed to become tuberculin positive. This parallelism between experimentally and clinically observable loss of virulence existed

in the years 1937, 1938 and 1940. Since 1931, the 423 BCG strain, used for vaccination in Denmark, has been kept on Sauton medium. These reductions in virulence of the BCG strain were also mentioned in a paper by J. Holm (2), where it is stated that "when such weakening eventuated, a new increase in virulence was obtained by several passages on bile potato."

Paradoxical as this statement may appear to any one familiar with BCG in particular and with bile cultures of tubercle bacilli in general, the high scientific standard of the distinguished Danish investigators and the scrupulous quality of their experimental work were sufficient reasons to scrutinize their assertions by experimental investigation.

A detailed report of the writer's researches in this matter has been published elsewhere (3). A brief outline of the findings is presented in this communication.

Five guinea pigs were inoculated intradermally at four different places (two on the right flank, two on the left) with 0.01 mg. and 0.0001 mg. of a 27-day-old culture of BCG on Sauton-potato and a 27-day-old culture of BCG on bile potato. In this experiment the bile culture caused precocious ulcerative reactions in the 0.01 mg. concentration; whereas injection of the other culture resulted in the usual node formation after the usual delay in only two of five animals.

Presumably this old culture contained numerous dead bacilli and hence evoked reactions which were less strong than usual. Thus, in this experiment the bile culture gave rise to very strong reactions in comparison with the normal one.

Four guinea pigs were then inoculated intradermally with Sauton-potato transplants of BCG which had gone through three, four and five passages on bile potato, respectively, and with a normal BCG culture maintained for 14 years on Sauton-potato (0.01 mg.). This time there was not the slightest difference between the reactions provoked by these four inocula.

Four guinea pigs received an intradermal injection of 0.01 mg. of (a) normal BCG, and (b) a culture of BCG which had been passed once on bile potato and once on Sauton-potato. In this experiment also the reactions were the same after each inoculum.

Finally six guinea pigs were inoculated the same way with normal BCG suspended in saline solution, and with normal BCG suspended in saline containing 10 per cent ox bile (0.01 mg.). The bile-containing suspension provoked violent reactions, whereas the normal saline suspension gave the usual type of reaction.

It appeared, therefore, that the violent reactions obtained in the first experiment were a result of the admixture of bile in the suspension of BCG prepared from a bile potato culture.

As Jensen expressly states that his vaccine emulsions were always prepared from a Sauton culture, inoculated from a glycerin potato culture which in its turn was a subculture from a bile-potato culture, the increased virulence he observed cannot evidently be attributed to the admixture of bile in his vaccine emulsions.

In the present experiments, no increase of virulence in the BCG culture was observed after one, three, four or five passages on bile potato.

Holm reports that "in more recent years, instead of bile-potato passages, a

more frequent transfer of the strain on Sauton medium (every seven to ten days) has been employed." He states that the virulence of the strain is assumed to be weakening when the developing rate of the bacillary veil on the surface of the Sauton medium is slowing down. When this phenomenon occurs, a higher rate of growth may then be obtained by more frequent transfers.

Another explanation exists for the described phenomenon of loss of virulence of the Danish BCG strain. As stated previously, this phenomenon is unknown at the Pasteur Institute where the strain in use is a descendant of the same no. 423 culture which Calmette sent to Copenhagen in 1931. Nevertheless, it is possible that such a diminution of the allergizing power of the Danish vaccine, coinciding with a slowing down of the developing rate of the BCG culture on Sauton, as observed by Jensen and Holm, might be a consequence, not of a weakening of virulence, but of a weakening of the *vitality* of the strain. If this were so, there would be an increase of dead or debilitated bacilli in the vaccine suspensions. Considering this explanation of the facts stated by Jensen and Holm, it is possible that more frequent transfers would be sufficient to obtain a higher rate of growth and a better allergizing effect of the BCG culture, as the number of living bacilli is increased by such frequent transfers.

It is possible that the reason the Danish investigators had such difficulties in maintaining the vitality of their BCG strain when this phenomenon has not been observed at the Pasteur Institute is because of the circumstance that in Copenhagen the strain is constantly maintained on Sauton medium. As emphasized previously, Sauton medium is excellent for the production of thick veils in the first generations, but must be condemned as a routine medium for the preservation of laboratory strains of *M. tuberculosis* in general and of BCG in particular. The above hypothesis may also serve to explain the paradoxical fact that in Copenhagen a return of the BCG strain to bile potato was sufficient to increase the virulence of the strain. Bile potato is an excellent medium on which bovine bacilli grow luxuriantly and, though eventually their *virulence* is impaired by this medium, their *vitality* does not suffer on it. Thus it is possible that the BCG strain, weakened by a long series of transplants on Sauton, recovered its vitality on bile potato and *ipso facto* yielded a better vaccine.

The writer has had the opportunity to make a comparative test of the Pasteur Institute strain and the Danish BCG strain, which Doctor Orskov had the kindness to send to Doctor Bretey. In comparison it was not possible to detect any difference between the two strains by intradermal injection in six guinea pigs.

Consequently, the different behavior of the two strains appears to be a question of culture medium. When cultivated on a suitable medium, the Danish and the Paris strains of BCG prove to have exactly the same virulence. The results, at least as far as these two strains are concerned, support Calmette's claim that BCG is a *virus fixe*.

#### SUMMARY

The most suitable culture medium for the preservation of BCG is Sauton-potato. Sauton liquid synthetic medium is excellent for a few passages to ob-

tain a rich harvest of bacilli for vaccine preparation, but impairs the vitality of the strain in the long run and is therefore improper for the preservation of BCG. Ox-bile potato, which, after a long series of passages, extinguishes the virulence of bovine tubercle bacilli, is suitable, however, for their maintaining their vitality in good form. Therefore, the observations of Jensen and Holm that BCG after many passages on Sauton loses its slight virulence on this medium, but may be restored to its former virulence by a few passages on bile potato, may be explained by the concept that the "vitality" rather than the "virulence" of the strain was affected.

#### SUMARIO

##### *La Conservación de la Cepa BCG*

El medio de cultivo más apropiado para la conservación del BCG es el d<sup>e</sup> patata-Sauton. El medio sintético líquido de Sauton es excelente para algunos pases a fin de obtener una rica cosecha de bacilos para preparar vacuna, pero afecta la vitalidad de la cepa a la larga, y resulta, por consiguiente, impropio para la conservación del BCG. El medio de patata-bilis de buey que, tras una serie larga de pases, extingue la virulencia de los bacilos tuberculosos bovinos se presta, sin embargo, para mantener su vitalidad en buena forma. Por lo tanto, las observaciones de Jensen y Holm, en el sentido de que BCG, después de muchos pases por Sauton, pierde su leve virulencia en ese medio pero puede recobrar su antigua virulencia con algunos pases por patata-bilis, pueden encontrar su explicación en el concepto de que se afecta la "vitalidad" más bien que la "virulencia" de la cepa.

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## EDITORIAL

### Lobectomy and Pneumonectomy in Pulmonary Tuberculosis

An evaluation of the efficacy of any therapeutic procedure employed in the treatment of a chronic disease may take many years. This is especially true when there is a considerable variation in the natural course of the same disease in different individuals. These statements apply particularly to the problem of lobectomy and pneumonectomy in the management of pulmonary tuberculosis.

There has been considerable divergence of opinion as to the place of pulmonary resection in the treatment of tuberculosis. Further experience is tending to clarify some of the controversial issues. Much of the earlier confusion concerning the results of lobectomy and pneumonectomy in tuberculosis may be ascribed to the following reasons: a short period of time had elapsed between the operation and the report; unwarranted assumptions were made as to the prognosis in a given case with other forms of therapy, particularly thoracoplasty; the postoperative sputum studies were often inadequate; and complete follow-up data were not always obtained. Now, however, the addition of streptomycin has necessitated a complete reorientation of the entire subject.

At present pulmonary resection would seem indicated for the following groups of patients with tuberculosis:

(1) When an adequately performed thoracoplasty has failed to produce cavity closure and convert the sputum, with the proviso that this does not necessarily include patients who have only an occasional sputum culture or gastric concentrate positive for tubercle bacilli.

(2) Stenosis of the main bronchus or a lobar branch bronchus is often an indication for resection. Cases with a narrowing of the bronchus due to swelling or granulation tissue, which might heal without marked stenosis following local treatment and collapse therapy, are not necessarily included. If streptomycin therapy is required in order to control the bronchial lesion, the advisability of resection while the beneficial effect of the streptomycin is present must be seriously considered.

(3) Bronchiectasis secondary to pulmonary tuberculosis when symptoms due to bronchial infection are present. Patients with recurrent hemoptysis from bronchial lesions are best treated by resection. The diagnosis of bronchiectasis is often made incorrectly, due to confusion between true bronchiectasis and the shortening and slight widening of bronchi which occur when a lung is collapsed. The bronchial distortion seen bronchographically, especially in the upper lobe after thoracoplasty, does not in itself constitute an indication for pulmonary resection.

(4) Primary lobectomy is preferable to thoracoplasty when cavities are situated in the basal portion of the lower lobe and the active tuberculous process is limited to the lower or middle and lower lobes. Temporary phrenic nerve interruption, pneumothorax, or pneumoperitoneum may have been given a trial first if there was little evidence of bronchial involvement. A cavity in the apex

of the lower lobe, however, is not necessarily an indication for resection as such a cavity may be closed by thoracoplasty, whereas, if resection is undertaken, a pneumonectomy is usually required because of involvement in the adjacent lower part of the upper lobe.

(5) Tuberculomas, when of sufficient size to warrant surgical therapy, are an indication for partial or total lobectomy. Many so-called tuberculomas are actually cavities filled with caseous material. Some solitary tuberculomas require removal because the diagnosis of tumor cannot be excluded.

(6) There has been considerable difference of opinion concerning the advisability of pulmonary resection in the treatment of tension cavities. In some cases one can be quite certain that a tuberculous cavity has a positive intracavitary pressure but in many other cases such a diagnosis based on the roentgen appearance alone may be incorrect. Moreover, a cavity which is under tension one day may have a relatively free bronchial drainage at another time. The response of so-called tension cavities to collapse procedures is unpredictable. If a collapse procedure is elected, thoracoplasty is usually preferable to pneumothorax because of the resultant immobility of the chest wall. Some cases with tension cavities have other lesions such as bronchostenosis which are an indication for primary resection. At present, a trial with thoracoplasty without streptomycin is indicated in some cases. The streptomycin should be reserved for the time of resection if the latter procedure is required.

(7) The relative merits of thoracoplasty and pneumonectomy in cases of very extensive unilateral tuberculosis have been debated at length. Should one proceed directly with pneumonectomy and follow with a limited thoracoplasty or should one first perform a complete thoracoplasty? The assumption that one can be certain that a thoracoplasty will fail to be of benefit in such a case is sometimes made without good justification. Although it is true that the likelihood of cavity closure and sputum conversion following thoracoplasty may be relatively small, nevertheless, an improvement in the patient's general condition and diminution in the amount and infectivity of the sputum may follow. Pulmonary resection, if then necessary, can be performed without much difference in the operative risk. At the same time some of the patients in this group may obtain such a satisfactory result from thoracoplasty that no further surgical procedure is required. The most important factor in this problem today hinges on the time when streptomycin is employed. In those cases with extensive unilateral tuberculosis in which the disease is sufficiently quiescent to permit a thoracoplasty to be undertaken without streptomycin, but where there is considerable question as to whether a thoracoplasty will be adequate, streptomycin should not be given at the time of thoracoplasty unless postoperative complications require. Otherwise one may be faced later with the necessity of performing a pulmonary resection on a patient with tubercle bacilli resistant to streptomycin. If it is felt that no major surgical procedure can be undertaken without the aid of streptomycin, and there is a considerable chance that a pneumonectomy will be required, it would seem best to proceed at once with resection while the maximum effect of streptomycin is obtainable.

Some of the confusion which has arisen in judging the relative place of pul-



monary resection and thoracoplasty in cases of tension cavities, upper lobe bronchiectasis, and caseous destruction of an entire lung, has been due to the meagre data that have been published of the results of thoracoplasty in lesions of this type. Various experienced observers have widely divergent impressions. There is an urgent need for the evaluation of the late results of thoracoplasty analyzed according to the type of lesion for which the collapse was undertaken.

Overdistension of the remaining pulmonary tissue following either lobectomy or pneumonectomy in the tuberculous patient seems to be disadvantageous. A thoracoplasty should be performed soon following pneumonectomy. Likewise, an upper stage thoracoplasty should usually be done in those cases in which a primary upper lobe lobectomy has been performed. An exception to this should be made when dealing with patients in the growing age period.

The introduction of streptomycin has necessitated a complete revaluation of the status of pulmonary resection in tuberculosis. The operative morbidity and mortality have been considerably reduced. When resections were performed without the benefit of streptomycin, there was a relatively high incidence of flare-up of the disease following operation. Many of these exacerbations were apparently transient and, on the basis of a few years follow-up, the late reactivations seemed to be of greater significance than the postoperative morbidity. A considerable percentage of the patients who subsequently had progressive tuberculosis, however, had not had an entirely uneventful postoperative course. One wonders, therefore, to what extent the late exacerbations will be reduced by the use of streptomycin in the operative period.

Removal of the major portion of the pulmonary tuberculous tissue does not seem to be immunologically more beneficial than collapse of the lung. It would therefore seem best at present to restrict lobectomy and pneumonectomy to those cases in which collapse therapy is inadequate. It cannot be foretold whether future developments in chemotherapy will radically alter the relative place of collapse therapy and excisional surgery in the treatment of pulmonary tuberculosis.

HERBERT C. MAIER

## LETTERS TO THE EDITOR

### BCG

To the Editors of the American Review of Tuberculosis:

Four years of German occupation have shut French scientific workers off from the outside world, and cut them from communication with their colleagues in free countries. After V-Day, British and American medical literature started to come in, trickle fashion first, but soon swelling into an avalanche of precious scientific information, which took us, hungry though we were, a lot of time to digest.

These preliminary lines may serve to explain why the work of Milton I. Levine and Margaret F. Sackett on BCG immunization in New York City (Am. Rev. Tuberc., 1946, 53, 5, 7) came to our knowledge only a few months ago. Since then, references to it in other scientific reviews showed us the impression the statements of Levine and Sackett have made on the minds of workers engaged in preventive vaccination against tuberculosis with BCG.

Before criticizing the article of Levine and Sackett, I want to do homage to the accuracy of their work and to the extraordinary amount of trouble they took to exclude all sorts of factors that might have influenced the disappointing results of their experiment. For it must be acknowledged that, from the point of view of our fight against tuberculosis by preventive vaccination, the figures they obtained are far from encouraging indeed.

The authors point out that W. H. Park's favorable results had suffered from a "tendency to inoculate children of the more intelligent and coöperative parents, and to keep the children of the non-coöperative parents as controls." Having eliminated this possible source of error, Levine and Sackett, continuing the investigation of W. H. Park along the same lines since January 1933, observed that the death rates from tuberculosis in vaccinated and nonvaccinated children are practically identical (1.41 and 1.51 per cent respectively).

We are the more impressed by these figures, as the authors have investigated different variable factors which might have influenced their results, and, having done so, exclude them all. The differences studied include: exposure to positive sputum between the two groups before and after January 1933; differences in racial distribution of vaccinated and control cases in the two periods; differences in economic conditions of the two groups before and after January 1933; possibility of a change in the number of lost cases before and after that date; variations in the number of autopsies in the two periods; and finally a loss of activity of the BCG vaccine.

But there is one particular point to which I would call attention. Summing up all cases of death from tuberculosis in vaccinated children that occurred during the two periods (three in Park's time; eight since January 1933), the authors say, "*all eleven cases except one were definitely exposed to virulent tubercle bacilli in their homes within five weeks before vaccination.*"

Now shouldn't this be the crux of the problem? Did not Calmette and Guérin, when they advocated BCG vaccination of humans, insist on the necessity of administering the vaccine before infection with virulent tubercle bacilli could have taken place, and, if possible, of separating the newborn babies from their infectious surroundings until the vaccine should have done its work, *i.e.*, during six weeks at least?

This most important condition not having been fulfilled, how could we be surprised at the meagre results of this campaign of preventive vaccination which involved such an amount of work? We may even be astonished by the favorable results of W. H. Park,

if they were obtained under the same faulty conditions as the authors claim. It seems probable indeed, that they resulted, at least in part, from an involuntary tendency to choose babies of intelligent, coöperative parents for vaccination, leaving the others as controls. I say "in part," for recent reports from Soviet Russia show that large scale BCG vaccination in that country resulted in a 50 per cent diminution of the tuberculosis mortality among infants since the beginning of this preventive measure. And the same reports state that separation of BCG vaccinated babies from their tuberculous surroundings is not practised. Thus even in such unfavorable conditions, BCG vaccination seems to exert noticeable protection against tuberculous infection in infants (S. Abolnik, *Ann. Inst. Pasteur*, 1947, 73, 373).

But there are so many reports from so many different countries the general note of which is so diametrically opposite to the outcome of Levine's and Sackett's investigation, that one cannot escape from the impression that there must be something at fault at the base of their pessimistic opinion. I only mention here the recent work on BCG vaccination among Indians by Aronson and his co-workers (*Am. Rev. Tuberc.*, 1942, 45, 41), the studies of Ferguson in Canada (*Am. Rev. Tuberc.*, 1946, 54, 325), Courcoux in Paris (*Rev. de la Tuberc.*, 1946, 10, 755), Heimbeck in Norway among nurses (*Tubercle*, Nov. 1936, 97), and the vast BCG campaign of Jensen and Holm in Denmark (*Pub. Health Rep.*, 1946, 61, 1298), in order to underline my assertion. As mentioned previously, a fundamental error has been committed by administering BCG to children, most of whom must be considered as having been probably contaminated, even if negative to Mantoux, before vaccination or shortly thereafter. Thus most of the authors' painstaking work has been done in vain.

Of course I understand that Levine and Sackett know as well as we do the fundamental necessity of separating babies from their tuberculous parents before and after BCG vaccination and that they were no doubt prevented from doing so by insurmountable difficulties. In fact, the figures they found in children, in whom such conditions could be fulfilled, are much more favourable.

The table on page 529 of the article of Levine and Sackett shows one tuberculosis death among 91 children separated three months before and three months after being vaccinated in contrast to three tuberculosis deaths among 96 nonvaccinated but equally separated children. And the following statement is made by the authors apropos of these findings: "It would appear from these figures that the inoculations with BCG might be of some protection if children were separated from the tuberculous environment for a sufficiently long period of time before and after vaccination."

Unhappily the number of these correctly separated cases is not sufficient to give irrefragable statistical evidence and the general impression left on the reader's mind by the article of Levine and Sackett is rather unfavourable to BCG. That is why it seems necessary, in the present circumstances, to point out why this unfavourable impression is not justified.

Their article shows at any rate and with evidence how an involuntary choice as to the children to be vaccinated may falsify the results of an investigation, and we must be thankful to the authors for having made this fact clear to us.

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October 6, 1947

To the Editors of the American Review of Tuberculosis:

I have carefully read the article of Dr. van Deinse analyzing the paper we published in 1946.

I might state immediately that we are in complete agreement with his contention that separation before and after vaccination is an essential factor in a well organized study on the efficacy of BCG.

This was pointed out clearly in our own paper, "Results of BCG Immunization in New York City," by Levine, M. I. and Sackett, M. F., which appeared in the American Review of Tuberculosis, 53: 517, June 1946, where it was stated (page 527): "The question naturally arises as to whether the deaths among the BCG vaccinated cases were due to a tuberculous infection previous to vaccination or whether the vaccination was an inadequate protection against a subsequent infection. This is difficult to answer." Moreover, on page 529 it was stated: "In the course of our studies a certain number of exposed children chanced to be separated for three months before and three months after vaccination. It is to this group, then, that we must look for any trend that might give an indication of the value of the inoculation."

The data which were presented in table 14 follow.

TABLE 14 (page 529)

*Exposed cases separated three months before and three months after being vaccinated or taken up*

|                 | NUMBER OF CASES | TUBERCULOSIS DEATHS |          |
|-----------------|-----------------|---------------------|----------|
|                 |                 | Number              | Per cent |
| Vaccinated..... | 91              | 1*                  | 1.1      |
| Controls.....   | 96              | 3**                 | 3.1      |

\* This child was born of a mother dying of tuberculosis; was never exposed; died at 3 months of age.

\*\* One case with no known exposure died of tuberculosis at 15 months of age.

Continuing (pages 529, 530): "It would appear from these figures that the inoculations with BCG might be of some protection if children were separated from the tuberculous environment for a sufficiently long period of time before and after vaccination. From a scientific viewpoint, in justice to BCG, its efficacy in preventing tuberculosis should be judged only from results of cases definitely not infected with human tubercle bacilli before vaccination and not exposed after vaccination until allergy has developed from the BCG administration."

Dr. van Deinse writes that: "A fundamental error has been committed by administering BCG to children who were already contaminated."

We did state in our article that all 11 cases (who were vaccinated and later died of tuberculosis) except one were definitely exposed to virulent tubercle bacilli in their homes within five weeks before vaccination. Nevertheless, these children were all tested up to 1.0 mg. tuberculin intradermally and only vaccinated when the test was found to be negative. Although these children may have been already infected with tubercle bacilli and may have been still in the pre-allergic phase, there is no definite evidence that such a condition did exist. These children may possibly have been infected shortly after vaccination.

No claim was made in our article as to proof for or against the value of vaccination

with BCG. Our only purpose was to present the results of the New York study and to observe critically certain other studies already published.

Our only conclusion was that "as a public health measure, the routine vaccination with BCG of children from tuberculous homes is less advantageous than removal of the tuberculous subject from the home."

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# THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

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**Drug Assay Method.**—An attempt to devise a rapid and economical method of assaying the tuberculostatic property of compounds resulted in the following procedure: serum of animals that had received the drug to be tested was incorporated in a liquid medium which was then inoculated with tubercle bacilli of human type. The presence or absence of an inhibitory action of a compound on the growth of the culture could be observed and its effect *in vivo* could be anticipated. This suggests a method for overcoming the usual discrepancy between the results of *in vitro* and *in vivo* testing of substances for their activity against the tubercle bacillus.—*Procedure for Distinguishing Drugs Effective against the Tubercle Bacillus by a Combined in vivo and in vitro Method*, E. F. White & A. G. Karlson, *Proc. Staff Meet., Mayo Clin., January 21, 1948*, 23: 52.—(P. Q. Edwards)

**Virulence of Tubercle Bacilli.**—It is almost unanimously agreed that the newly formed tubercle bacilli growing on artificial culture media do not all become acid fast until about the fifth or sixth day of their development. What degree of virulence the germs have in this early period of their existence is not well known. It has, however, been shown recently that during the first five days of their growth in Sauton's synthetic media, tubercle bacilli are definitely less virulent than in older cultures. The author followed the development of pathogenicity of bovine tubercle bacilli developing in the upper levels of a liquid culture medium such as the egg medium of Besredka, following the inoculation of the lower portion with tubercle bacilli introduced

through a glass tube. The germs developing at the upper levels of the medium would all be young, those introduced to start the culture remaining lower down. Samples were removed from the middle level after two, three, four, five, six, and twenty-one days. No acid-fast bacilli were found until after the second day. It was consequently assumed that samples removed on the third day would contain young bacilli. Dilutions of the samples in physiologic salt solution were made in various strengths (1:5, 1:10, 1:100, etc.). One-tenth cc. of each was planted on Lowenstein's medium, and 1 cc. was injected subcutaneously into guinea pigs and intravenously into rabbits. The number of bacilli in one cc. of each dilution was determined by counting the number of colonies that developed on the Lowenstein's medium. The lesions which developed in the animals inoculated with a corresponding number of germs made possible a comparison of the virulence of young germs (three to four days' growth) and older ones (six to twenty-one days). It was found that the difference was slight if only a small number of bacteria (less than 100) was employed. To secure more definite proof it was necessary to inoculate at least 100 to 500 bacilli; better results were secured when more than 500 were used. The guinea pigs and rabbits inoculated with bacilli removed from the medium on the third or fourth day of their development were examined postmortem, six weeks to three months after their inoculation. Very few tubercles were found anywhere, and the organs were apparently normal. On the other hand, animals inoculated with corresponding quantities of older bacilli (six days) and sacri-

ficed after the same period of waiting, had many tubercles in various organs. Their lesions were much more serious than those caused by bacilli three or four days old but not as extensive as those caused by bacilli twenty-one days old. In the latter case the tubercles were often confluent and generalized through all the organs. The author concludes that young bacilli in the first week of their growth have less virulence than those three weeks old. The pathogenicity which then characterizes them begins about the sixth day. The period during which the germs have only slight virulence corresponds with that during which many of them have not yet become acid-fast. These experiments are similar to those made by other workers, including P. Hauduroy (*Le probleme des tuberculoses atypiques*, Lausanne, 1946) who believes that the tubercle bacillus goes through an evolutionary cycle and that old and degenerating bacilli may also lack acid-fastness.—*Etude de pouvoir pathogene des bacilles tuberculeux*, L. Nègre, *Selection*, April, 1947, 1: 208.—(A. T. Laird)

**Experimental Tuberculosis in the Syrian Hamster.**—On account of the expense of feeding guinea pigs and rabbits, their slow rate of reproduction and the care required to rear them, the author, who is laboratory chief of the Laval Hospital in Quebec, has experimented with the golden or Syrian hamster (*Cricetus Auratus*). This is a small rodent of the Muridae family, somewhat smaller than a Norway rat. The animal is about 30 cm. in length, has a short tail and is provided with two capacious pouches beginning one in each cheek and extending to its shoulders, which it stuffs with grain to store for the winter. It lives in underground passages where it hibernates. It is easy to care for, neat and clean, and in captivity it is omnivorous. Other advantages which it presents for experimental work is its short period of gestation, sixteen days, and the number of its offspring, from 5 to 11 per litter. These periods occur in rapid succession until hibernation which, however, lasts for about six months. It is relatively gentle if carefully handled. The animal has

been used to some extent in the study of tropical diseases and parasitic infections. The author wished to determine its suitability for use in studying tuberculosis. The three animals of a first group, weighing about 110 grams each, were given subcutaneous injections of 0.1 mg. of a strain of human type bacilli of average virulence. Infection proceeded very slowly and generalized tuberculosis developed only after three months. A second group of five was inoculated with 0.5 mg. of a virulent bacillus which had been used previously in experiments with guinea pigs and rabbits. They were killed after intervals varying from fifteen days to four months. Tuberculosis developed slowly in this group also. The third group of five animals was inoculated with 0.5 mg. of a strain of bovine type tubercle bacilli. These animals showed a more rapid development of tuberculosis. The author concludes that the Syrian hamster is not as useful for animal inoculation with tuberculosis as the guinea pig, but that it might be employed with advantage in differentiating the human and bovine types of tuberculosis. His findings confirm those of previous observers.—*Tuberculose experimentale du hamster dore*, M. Giroux, *Laval med.*, October, 1947, 12: 865.—(A. T. Laird)

**Serum Albumin and Tween Medium.**—It has been previously reported that although the presence of commercial Tween 80 (an ester of oleic acid) facilitates submerged growth of tubercle bacilli in liquid media, initiation of growth with small inocula requires the addition of serum albumin. It was also found that the chief inhibitor of growth against which the albumin protects the tubercle bacilli is some unesterified oleic acid present in the commercial Tween 80 and further released from it during incubation. In the present paper the bacteriostatic effect of Tween 80 and the growth promoting effects, if any, of other proteins are reported. Also the effect of albumin on surface growth was studied. Direct proof that the Tween 80 molecule itself is not bacteriostatic was obtained by the preparation of material essentially free from fatty acid. Tween

80, freed of contaminating fatty acid, not only permitted growth of small inocula, but protected against small amounts of added oleic acid. It is unlikely that serum albumin in itself offers any nutriment for the tubercle bacillus. It is a protective bacterial growth factor; by binding traces of fatty acid in the medium it permits the unmolested growth of the smallest possible inoculum of tubercle bacilli. It is likely that the growth promoting effect of serum albumin on surface growth, when added to Long's synthetic medium (which contains no Tween), is due to its ability to bind the traces of fatty acid often present. For this purpose undenatured albumin is required. Crystalline beta-lactoglobulin has a smaller capacity, and a number of other proteins have no perceptible capacity to bind oleic acid.—*The Binding of Fatty Acids by Serum Albumin, a Protective Growth Factor in Bacteriological Media*, B. D. Davis & R. J. Dubos, *J. Exper. Med.*, September, 1947, 86: 215.—(J. S. Woolley)

**Effect of Lipase on Bacterial Growth.**—Serum albumin is essential for the initiation of growth by small inocula of tubercle bacilli in a liquid medium containing "Tween 80" which promotes submerged growth of these organisms. The albumin acts as a protective rather than a nutritive growth factor binding traces of unesterified fatty acid which inhibit growth of small inocula. The hydrolysis of "Tween 80" by lipase in commercial albumin releases free fatty acid in bacteriostatic quantities exceeding the binding capacities of the albumin. Elimination of lipase permits the cultivation of small inocula such as 2 or 3 bacteria. Lipolysis was also found to account for the bacteriostatic effect of several materials of biological origin (serum, bacterial culture filtrates) observed only in media containing "Tween 80." The effect can be eliminated by the destruction of the lipase by heating at 56 C, by the use of commercial crystalline bovine serum albumin which is not perceptibly contaminated by lipase or by the addition to the medium of 0.01 per cent NaF, which inhibits lipase but is not bacteriostatic to the

tubercle bacillus. The effect can also be overcome by the use of a high concentration of albumin. Lipolytic activity also accounts for the bacteriostatic effect in this medium of horse serum and of a culture filtrate of *M. phlei*. This experience emphasizes the importance of guarding against lipolytic effects when materials of biological origin are introduced into a Tween-containing medium for diagnostic work (e.g., blood culture) or chemotherapeutic studies (e.g., impure antibiotics). The use of "Tween 80" and tubercle bacilli provides an exceedingly sensitive bioassay for lipase. Although the bacteriological work was confined to human type tubercle bacilli, the principles evolved are applicable to the cultivation, in the presence of esters, of any bacteria that are sensitive to free fatty acid.—*The Inhibitory Effect of Lipase on Bacterial Growth in Media Containing Fatty Acid Esters*, B. D. Davis & R. J. Dubos, *J. Bact.*, January, 1948, 55: 11.—(F. G. Petrik)

**Nature of Acid-fastness.**—Evidence is presented which suggests that the property of acid-fastness of the tubercle bacillus is dependent upon the permeability of the cytoplasmic membrane. When the bacillus is stained by the Ziehl-Neelsen method the dye gains entrance into the cell through this membrane where a small portion of the dye is firmly absorbed by the cytoplasm and the remainder is free. The free dye can be removed by immersion in boiling neutral 50 per cent alcohol or boiling water without altering the acid-fast property. In the presence of "Tween 80" the dye is removed in thirty to sixty seconds as compared with five to seven minutes in the absence of Tween and more rapidly in boiling alcohol than in boiling water. The free dye can be precipitated to form beads and these bodies are often greater in diameter than the width of the cell. The location of beads cannot be predicted before formation, nor can evidence of their previous location be found after their dispersal. When reformed they may be found in their original location, but just as often they occupy new positions in the cell. The granular form may be stained to show



beading but it was noted that the dye accumulates and is dispersed only in the granular portions and not in the unstained interspaces. The fact that tubercle bacilli are rendered non-acid-fast by trauma, autolysis, or the use of acid is satisfied by the proposed theory: the action has been so severe that the cytoplasmic membrane no longer controls permeability with relation to the dye used. Free dye can be accumulated and redistributed in acid-fast mushroom spores showing that this phenomenon is not peculiar to mycobacteria.—*The Nature of Acid-Fastness*, D. Yegian & R. J. Vanderlinde, *J. Bact.*, December, 1947, 54: 777.—F. G. Petrik)

**Proteins of the Tubercle Bacillus.**—The purpose of this paper is to provide data from electrophoresis experiments concerning the insoluble residue of tuberculin, this being the fraction left after extraction by water and alcohol-ether mixtures. The extraction and electrophoresis methods are described in detail. The principle fractions found in the residue mixture were identified as nucleic acid, a protein, and a carbohydrate. The protein has a very high tuberculin activity.—*Physico-chemical Analysis of Protein Antigens Isolated from the Tubercle Bacillus*, II, A. Grönwall, *Upsal läkaref. förh.*, June 30, 1947, p. 227.—(R. W. Clarke)

**Passive Transfer of Tuberculin Sensitivity.**—Homologous passive transfer of tuberculin sensitivity was accomplished with the peritoneal and splenic cells of guinea pigs infected with BCG strain of *Mycobacterium tuberculosis*. Intense reactions were elicited in the recipients with dilution of Old Tuberculin as high as 1:100. Animals receiving splenic cells were usually less sensitive. The duration of the tuberculin sensitivity was for only a few days and was accomplished only with living cells and after an incubation period of two to three days. This suggests that the sensitivity may be principally due to antibody elaborated by such cells during their residence in the recipient.—*The Tuberculin Reaction: I. Passive Transfer of Tuberculin Sensitivity with Cells of Tuberculous Guinea Pigs*, W. F. Kirch-

heimer & R. S. Weiser, *Proc. Soc. Exper. Biol. & Med.*, October, 1947, 66: 166.—F. B. Scibert)

**Passive Transfer of Tuberculin Type Hypersensitivity.**—The tuberculin type of hypersensitivity was transferred passively to normal, unsensitized guinea pigs by injection of the cells of peritoneal exudate, lymph nodes, spleen and whole blood of tuberculin-sensitive guinea pigs. The passively conferred sensitivity lasted four or five days. Positive results, employing suspensions containing 95 per cent of lymphocytes, suggest that this cell type may be of great importance in the transfer of sensitivity.—*Passive Cellular Transfer of the Tuberculin Type of Hypersensitivity*, A. B. Stavitsky, *Proc. Soc. Exper. Biol. & Med.*, February, 1948, 67: 225.—F. B. Scibert)

**Lympholysis by Tuberculin.**—Mature lymphocytes from the blood or spleen of normal mice are not lysed by tuberculin or by the soluble substances derived from cultures of *S. enteriditis*. Lymphocytes from mice infected with tuberculosis or *S. enteriditis* are lysed specifically by the respective products from these organisms. Lympholysis of mouse cells can be blocked by adequate amounts of phosphate buffer at pH 7.2, by 0.5 per cent bovine albumin in saline, or by saline alone. Lympholysis of tuberculous guinea pig cells can be blocked by phosphate buffer or in complement-poor suspending fluids. Mouse granulocytes, monocytes and acute splenic tumor cells are not affected by the specific lytic agent before or after lympholysis. In the guinea pig, lympholysis is followed by destruction of granulocytes and monocytes as well as some of the remaining lymphocytes. Specific lympholysis can also be demonstrated in fresh heparinized mouse or guinea pig blood.—*Lytic Effect of Bacterial Products on Lymphocytes of Tuberculous Animals*, C. B. Favour, *Proc. Soc. Exper. Biol. & Med.*, June, 1947, 65: 269.—F. B. Scibert)

**Effect of Pneumotropic Virus on Pulmonary Tuberculosis in Mice.**—Healthy mice may harbor in their lungs one or more viruses in a

latent state. A second infection may serve to provoke or activate these agents and thus be affected by their presence. Experimental tuberculosis in mice might thus be influenced by the concurrent development of infection with a latent virus. To determine the effect of active virus on the course of experimental tuberculosis (pulmonary), mice were infected with both virus and bacilli. The infecting bacillus was H37Rv given intraperitoneally. The viruses used were a strain of pneumonia virus of mice (PVM15) and an influenza A virus (PR8), both administered intranasally. Two strains of albino mice, both similarly susceptible to tuberculous infection, were employed. In the first series of experiments the virus and the bacilli were given almost simultaneously, the virus in various strengths and the bacilli usually in the same amount. A control group received no virus. At the end of 3 weeks all surviving mice were killed. It was found that of the animals receiving tubercle bacilli alone, 17 per cent showed pulmonary lesions (score ratio = 0.061), whereas of those receiving tubercle bacilli and a full dose of PVM, 73 per cent showed definite tuberculous lung lesions with a score ratio of 0.329. A tenfold decrease in the amount of the virus inoculated did not decrease the effects of the viral infection on the course of the tuberculous infection. A decrease of 100-fold in the amount of virus inoculated caused some decrease in its effect which was, however, still substantial. The influenza virus was also found to enhance pulmonary tuberculosis in mice in a manner analogous to infection induced with PVM. The viruses employed were diluted in broth containing inactivated horse serum. The intranasal instillation of the diluent alone apparently had no enhancing effect on the pulmonary tuberculosis, but when fresh human serum was used there was much enhancement of the pulmonary lesion. It seems probable that this activates the PVM latent in the mouse lung. In another set of experiments the virus was not administered to the mice until three weeks after infection with tubercle bacilli. As it was necessary that the animals live longer than in the previous experiment the dosage of tubercle bacilli was considerably less.

The overall length of the experiment was six weeks. Even under these conditions the instillation of PVM or PR8 increased both the incidence and extent of pulmonary tuberculous lesions. When the inoculum of tubercle bacilli was very small neither virus caused any definite alteration in the course of the tuberculous process. Microscopic examination showed no significant qualitative differences between the tuberculous lesions in the lungs of mice which received tubercle bacilli alone or tubercle bacilli plus the viruses. However, striking quantitative differences were observed as indicated by the scoring. There was no doubt of the tuberculous nature of the lesions seen for, besides their typical histological appearance, tubercle bacilli were often present in tremendous numbers. The lesions induced by either of the viruses are very different from those caused by tubercle bacilli and can be readily recognized. The course of pulmonary tuberculosis in the mouse appears to be accelerated as a result of concurrent infection of the lung with either of the two pneumotropic viruses studied. This effect is obtained with virus inocula sufficiently small as to induce little or no definite viral pneumonia.—*The Enhancing effect of Concurrent Infection with Pneumotropic Viruses in Pulmonary Tuberculosis in Mice*, M. Volkert, C. Pierce, F. L. Horsfall, Jr. & R. J. Dubos, *J. Exper. Med.*, September, 1947, 86: 203.—(J. S. Woolley)

**Recovery in Experimental Friedländer's Bacillus Pneumonia.**—Recent studies of the mechanism of recovery in pneumococcal pneumonia have shown that "surface phagocytosis" can bring about destruction of pneumococci in the lung in the absence of type-specific immune bodies. The present investigation deals with Friedländer's bacillus pneumonia in rats. Friedländer's bacillus and the pneumococcus are both encapsulated organisms, the former is Gram-negative and the latter Gram-positive, and their immune reactions are similar. This, the first of three papers dealing with the mechanism of recovery in experimental Friedländer's pneumonia, discusses the evolution of the disease. Pneumonia was produced in white rats by the

intrabronchial inoculation of the bacilli suspended in mucin. The pneumonia was lobar in type, was almost universally fatal, and simulated the acute form of the natural disease in human beings. The pathogenesis of the pneumonic lesion was studied by examination of the lungs of animals killed at frequent intervals during the course of the infection. Histologically the various stages of the pneumonia were essentially the same as in experimental pneumococcal pneumonia except for the following differences: (1) In isolated areas in Friedländer's pneumonia many more bacteria were encountered in the alveoli than were ever noted in the pneumococcal pneumonia. (2) Abscess formation was common in the late stages of Friedländer's infection, whereas it was not noted in the pneumococcal lesion. (3) Organization of the alveolar exudate, rarely observed in experimental pneumococcal pneumonia, was a prominent feature of the pneumonia due to the Friedländer's bacillus. The mechanism of spread of the Friedländer's lesion appeared to be the same as that of pneumococcal pneumonia, *vis.*, by way of infected edema fluid. Likewise there was noted the same phagocytosis of organisms in the lungs of even bacteremic animals dying of the infection.—*Studies on the Mechanism of Recovery in Pneumonia Due to Friedländer's Bacillus: I. The Pathogenesis of Experimental Friedländer's Bacillus Pneumonia*, L. Sale, Jr. & W. B. Wood, Jr., *J. Exper. Med.*, September, 1947, 86: 239.—(J. S. Woolley)

**Recovery in Experimental Friedländer's Bacillus Pneumonia.**—Both clinical and experimental studies indicate that infections due to Friedländer's bacillus may be favorably affected by sulfonamide chemotherapy. The present report (part II of the studies on recovery) deals with the effect of such chemotherapy upon the pulmonary lesion in experimental Friedländer's pneumonia in rats. Sulfadiazine and sulfamerazine were administered through a blunt cannula by way of the mouth. When treatment with either of these drugs was begun 6 hours after inoculation, more than 90 per cent of the animals survived this otherwise

fatal form of pneumonia. When treatment was delayed as late as 18 hours none of the animals survived. In those recovering most of the pneumonic lesions cleared completely, but an occasional animal exhibited small residual abscesses in the previously consolidated lungs. The recovery process in the lungs was studied histologically at various intervals during the therapy. As in the case of pneumococcal pneumonia, the principal action of the sulfonamide was upon the bacteria in the zone of advancing edema at the periphery of the pneumonic lesion. The drug appeared to stop the spread of the pneumonia, and the Friedländer bacilli were ultimately ingested and destroyed by the phagocytic cells in the alveolar exudate. Once phagocytes have accumulated in sufficient number in the infected alveoli, they destroy the bacilli by the same phagocytic process that operates in the zone of consolidation in untreated animals. The phagocytosis of bacteria in the lungs is apparently unrelated to the presence of antibody (opsonin) in the blood, for it occurs before antibody has had time to develop.—*Studies on the Mechanism of Recovery in Pneumonia Due to Friedländer's Bacillus: II. The Effect of Sulfonamide Chemotherapy upon the Pulmonary Lesion of Experimental Friedländer's Bacillus Pneumonia*, L. Sale, Jr., M. R. Smith & W. Barry Wood, Jr., *J. Exper. Med.*, September, 1947, 86: 249.—(J. S. Woolley)

**Recovery in Experimental Friedländer's Bacillus Pneumonia.**—As reported in part II, encapsulated Friedländer's bacilli are destroyed by leucocytes in the pneumonic lungs of rats in the absence of circulating or local antibody. In a series of delicate experiments it is now shown that this is brought about by the same "surface phagocytosis" which operates in the case of the Type I pneumococcus under similar conditions. Direct observation of the phagocytic process reveals that leucocytes in the lung can phagocytose unopsonized Friedländer's bacilli only by trapping them against the surfaces of alveolar walls, or by pinning them against the surfaces of ad-

jacent leucocytes. Evidence is presented that the bacilli thus phagocytosed are rapidly killed in the cytoplasm of the phagocytic cells. The failure of prolonged chemotherapy to cure the lung abscesses that not infrequently complicate Friedländer's pneumonia is apparently due to the facts that, in the absence of normal alveolar walls, surface phagocytosis is relatively inefficient, and in addition the absence of oxygen renders the phagocytes sluggish or even nonviable.—*Studies on the Mechanism of Recovery in Pneumonia Due to Friedländer's Bacillus: III. The Role of "Surface Phagocytosis" in the Destruction of the Microorganisms in the Lung*, M. R. Smith & W. B. Wood, Jr., *J. Exper. Med.*, September, 1947, 86: 257.—(J. S. Woolley)

**Bacteriophage for *Mycobacterium smegmatis*.**—A bacteriophage specific for *M. smegmatis* was isolated from samples of compost and soil by specific enrichment with a heavy washed suspension of *M. smegmatis*.—*A Bacteriophage for Mycobacterium smegmatis*, Grace M. Gardner & R. S. Weiser, *Proc. Soc. Exper. Biol. & Med.*, October, 1947, 66: 205.—(F. B. Seibert)

**Insulin Tolerance in Amyloidosis.**—Insulin tolerance tests were given to 7 patients with amyloidosis and 7 patients with cirrhosis, all tuberculous, in an attempt to determine if hepatic dysfunction were the sole cause of insulin resistance and impaired response to hypoglycemia usually demonstrable in amyloid disease. Although the effects of impaired nutrition and/or infection could not be definitely ruled out in influencing the results, insofar as similar insulin resistant curves were demonstrated in both groups, the conclusion is warranted that in amyloid disease impairment of liver function is responsible for the increased insulin resistance.—*The Insulin Tolerance Test in Amyloidosis*, S. London, *Quart. Bull. Sea View Hosp.*, April, 1947, 9: 137.—(P. Q. Edwards)

**Roentgenology at the University of Michigan** for cataloguing permanent X-ray records in order to facilitate their profitable use for research and teaching. Indexing and cataloguing is carried out at the time of each patient-visit and, since the observations are to be translated into a numerical code, the tabulation provides a clear picture of their actual practical importance and forces the radiologist to avoid loose, meaningless, ambiguous statements and to phrase his comments in terse, meaningful English. The roentgenological findings are broken down into ten anatomical divisions. All statements are filed in ten diagnostic categories, and within each category all entries are segregated in separate varieties by means of punch cards and sorting machines. At the end of each year, the catalogued material is printed by a mechanical tabulating machine, 50 entries to a page, and bound into four volumes. For each individual patient, a separate coded entry is made; an asterisk is used to indicate a case of "special interest". For cataloguing these cases, Special Interest pages are provided in the index; carbon copies of the original X-ray findings follow the index in loose-leaf form.—*Cataloguing X-Ray Experiences*, F. J. Hodges, *Publ. Health Rep.*, August 1, 1947, 62: 1129.—(O. Pinner)

**Abnormal X-ray Findings.**—The authors warn against confused thinking in mass radiographic programs. Pulmonary tuberculosis should not be diagnosed on the basis of one original X-ray film alone. If no tubercle bacilli are found the diagnosis should be "suspected tuberculosis", and if, in addition, the tuberculin test is negative, other reasons than tuberculosis must be found even for strongly suggestive shadows, including cavities. A provisional guide for disposition of persons with abnormal pulmonary X-ray findings, based on recent extensive experience in the United States and Denmark, is presented for use by the Tuberculosis Control Division, U. S. Public Health Service. Prerequisites for proper diagnosis are: (1) examination for tubercle bacilli; (2) identification of cavity on a 14" x 17" film, classifying lesions as present,

**X-Ray Cataloguing.**—This is a description of the system employed in the Department of

suspected, or absent; (3) tuberculin test; (4) evaluation of principal symptoms, i. e. temperature elevation, fatigue, and loss of weight. The routine procedure to be used during the one to three visits necessary to obtain and evaluate the four types of findings is described. The Guide shows nine principal groups into which the results of a person's examination may fall according to the presence, absence, or coexistence of the several findings, and outlines, for each of these groups, the follow-up and disposition of cases. The same methods are used for contacts with abnormal X-ray findings, whereas different procedures are used for follow-up and disposition of those contacts who have no abnormal X-ray findings. No person is told that he has tuberculosis unless a positive tuberculin test and bacillary findings have corroborated the "suspected tuberculosis" on the film. No person merely suspected is sent to a sanatorium. Even if he has symptoms, he can be observed in a clinic or local hospital. Thus he is spared psychological trauma and the risk of unwarranted hospitalization, and scarce sanatorium beds are reserved for infectious cases.—*Guide for Disposition of Persons With Abnormal Pulmonary Findings on X-ray Films*, H. E. Hilleboe & J. Holm, *Journ.-Lanc.*, June 1947, 67: 234.—(O. Pinner)

**Radiological Differentiation between Pericardial Effusion and Cardiac Dilatation.**—In spite of the growing knowledge of the morbid anatomy and pathological physiology of the pericardium, the diagnosis of pericardial effusion has remained the perplexing problem that it has always been. In the author's experience two stages of pericardial effusion are not readily diagnosed: the early fluid accumulation which does not as yet display the classical symptoms, and the extreme filling of the pericardial sac, which must be differentiated from the heart enlargement due to rheumatic involvement, thyrotoxicosis, myxedema, and various types of myocardial damage. In reference to the early roentgenologic recognition of pericardial effusion, certain statements are generally accepted: (1) that smaller amounts

of fluid, up to 250 or 300 cc., are usually not detectable fluoroscopically or on films; (2) that with the means available today it is not possible to differentiate between the heart shadow and the pericardial fluid shadow on the basis of difference in density. Even these fundamental rules will have to be revised, since with modern electric devices the limit of our perceptibility is constantly advanced and percussion and auscultation become the tools of another age. The author investigates, to good advantage, the value of the Valsalva test, apparently not previously applied to the problem. The dilated heart shows more marked changes in size and shape than the heart enclosed in pericardial fluid or even the normal heart. In changing from the Valsalva to the Mueller test, the weak pulsations of the dilated heart increase and become visible. In the presence of pericardial effusion, such pulsatory changes do not occur in equal measure. Observation of the angle of the bronchial bifurcation is further suggested as a diagnostic aid. Its visibility is frequently obscured in pericardial effusion. Visibility and widening to 100° to 130° favor a diagnosis of auricular enlargement or hilus tumor. Absence of lateral and posterior displacement of the esophagus, or a rather shallow, wide curved pressure zone along the whole length of the lower esophagus favors the diagnosis of pericardial effusion. Lateral and posterior displacement and localized auricular impression favor cardiac enlargement. Diminution or absence of cardiac pulsation is an important diagnostic sign of pericardial effusion, demonstrable by kymography.—*Radiological Differentiation between Pericardial Effusion and Cardiac Dilatation*, J. Arendt, *Radiology*, January, 1948, 50: 44.—(G. F. Mitchell)

**Hilar Densities Simulating Neoplasms.**—The value and importance of serial roentgenograms in establishing a diagnosis of pulmonary carcinoma after making use of all informative aids, such as history and bronchoscopy, is stressed. Hilar densities as found in single posteroanterior chest films is the chief concern of the author. Films showing hilar den-

sities of central pneumonia, Loeffler's eosinophilic pneumonia, primary hilar tuberculosis, lung abscess, and delayed resolution of pneumonia, all simulating bronchogenic carcinoma, are discussed. Roentgenograms in such cases may pattern themselves very closely after the early stages of the hilar type of bronchogenic carcinoma including, as well, progression into cavernous and pneumonic types. The radiologist, when interpreting hilar densities of this type, should not make an etiologic diagnosis on the basis of a single roentgenogram, since there are no criteria pathognomonic of the neoplastic lesion described in this paper.—*Hilar Densities Simulating Neoplasms*, C. Gottlieb & H. S. Sharlin, *Radiology*, January, 1948, 50: 57.—(G. F. Mitchell)

**Friedländer's Pneumonia in Infancy.**—Pneumonia caused by *K. pneumoniae* occurs with extreme rarity in infants and children. Only 4 cases have been reported in the literature. There are two possible types of lung infection: a lobar form very much like pneumococcus pneumonia, and a chronic form similar to tuberculosis. The chronic form may follow the acute infection. Diagnosis is usually a bacteriologic matter, and is usually a surprise. A case is reported of an undernourished infant who had required resuscitation at birth. On the third postnatal day it was noted to be doing badly, and to have a thick yellow mucoid discharge from the nose and throat. On the nineteenth day, inspiratory râles were heard at the apices, a leucocytosis was present, and an X-ray film showed clouding in the apices and globular densities in the right mid-lung and left basal areas. Penicillin and sulfadiazine were given for several days, and the râles cleared. In a few days a fever began, and the medication was repeated without effect. At the same time a culture from the nose and throat revealed *K. pneumoniae*. Streptomycin was immediately started in place of the other drugs, 0.67 g. daily in 8 divided doses, and this was continued for ten days. The fever dropped at once, the clinical condition began to improve steadily, and the X-ray densities began to clear. The cultures be-

came negative in two and a half weeks, the râles cleared somewhat, but large cystic rarefactions became visible in both lung fields by radiography. These "cavities" were still present a month after the cultures became negative, and while the infant was home in apparently good health. The more frequent use of cultures in the pneumonias of infancy will doubtless reveal more cases, and allow a selective use of the available drugs.—*Friedländer's Pneumonia in Infancy*, B. W. Miller, H. W. Orris & H. H. Janis, *J. Pediat.*, November, 1947, 31: 521.—(W. H. Oatway, Jr.)

**Staphylococcal Pneumonia.**—Primary staphylococcal pneumonia is one of the gravest forms of staphylococcus infection in childhood. The authors report 55 sporadic fatal cases with necropsies in children under the age of 7 years, seen in a general hospital; two-thirds were under 6 months of age. A series of 16 fatal cases in a nursery epidemic also are reported. The epidemic form often is associated with outbreaks of virus influenza. The sporadic form is predominantly a children's disease, occurring particularly during the neonatal period. In the 55 sporadic cases, pulmonary consolidation was the predominant feature in 45; in the other 10 cases, the pneumonia was associated with suppurative bronchitis and bronchiolitis; there was acute bronchiectasis in 2 and pulmonary abscess in 3 cases. The consolidation varied from a dark-red hemorrhagic pneumonia simulating the lobar type both in appearance and distribution to a diffuse gray pneumonia with suppurative softening which sometimes amounted to a localized abscess. The simple type was seen in 10 cases; in these, the duration of illness had been less than two days. If the illness had lasted longer, it was common to find early suppurative changes. Fibrinous pleurisy was seen in 16 and empyema in 26 cases. The empyema was usually unilateral. Pyopneumothorax was seen in only one and purulent pericarditis in 2 cases. There were no metastatic abscesses. The microscopic changes varied in accordance with the macroscopic. Where the condition grossly was

mainly hemorrhagic consolidation, microscopic examination showed groups of alveoli packed with red cells. At the margins, alveoli contained fibrin-free edema fluid with occasional phagocytes and clusters of gram-positive cocci. In cases which had survived a few days, there were suppurative foci, often with bronchitis, bronchiolitis and extensive infiltration and destruction of the bronchiolar walls. The nursery outbreak involved mostly premature infants. The children were healthy at birth but many mothers and nurses had influenza. They underwent sudden collapse a few days after birth and died in twenty-four to forty-eight hours. The pneumonia was diffuse in 12 and localized in 4 cases. Of the 12, 6 were hemorrhagic, 5 had ordinary non-suppurative bronchopneumonia and 1 had multiple abscesses. The other 4 also had multiple abscesses. None had empyema. The bronchi were free of inflammation and exudation. Microscopically, there were areas of hemorrhagic and suppurative pneumonia with purulent bronchitis and bronchiolitis. Staphylococci were found in the throats of many nurses. The milk supply was found to be uncontaminated. The infection is bronchogenic in origin. Diagnosis is difficult. Valuable time is lost in waiting for the uncertain results of bacteriological studies. The authors recommend immediate institution of oral and intramuscular penicillin therapy, supplemented by sulfadiazine and oxygen.—*Staphylococcal Pneumonia in Childhood*, K. J. Guthrie & G. L. Montgomery, *Lancet*, November 22, 1947, 2: 752.—(A. G. Cohen)

**Meningococcal Pneumonia.**—This is a rare condition. In one month, 2 cases were seen. There was no meningitis in either case. In one, meningococci were found in the bloodstream, but not in the sputum. In the other, the organism was recovered from both sputum and pleural fluid.—*Meningococcal Pneumonia*, I. B. Brick, *New England J. Med.*, February 26, 1948, 238: 289.—(A. G. Cohen)

**Therapy of Pertussis and Pneumonia.**—Twenty-six infants with uncomplicated per-

tussis were given hyperimmune gamma globulin (2.5 cc. daily for four days intramuscularly); no case developed pneumonia, no case died, and two-thirds had a good or excellent response. Twenty-six infants with pertussis and pneumonia were treated with the globulin and with 130 mg. of sulfadiazine per kilogram per day by mouth; most of these were very ill when first seen. Two died (7.7 per cent), but neither death could be attributed to failure of therapy. The recovery of the others was often dramatic.—*The Treatment of Pertussis and Pneumonia Complicating Pertussis: The Role of Hyperimmune Gamma Globulin and Sulfadiazine*, H. Brainerd, *J. Pediat.*, January, 1948, 32: 80.—(W. H. Oatway, Jr.)

**Streptomycin for H. Influenzae Empyema.**—Pneumococci cause 75 to 80 per cent of empyemas, and staphylococci and streptococci account for all but 1 per cent of the remainder. *H. influenzae* is one of the rare pleural invaders, and only a few instances of streptomycin therapy have been reported. The case is reported of a girl, aged ten years, who was seen a month after the onset of a respiratory illness with pneumonitis, empyema, mild cardiac decompensation, and evidences of cerebral and renal embolism. After a good initial response to penicillin the influenza bacilli became resistant. Large doses of streptomycin (250,000 units every three hours for a total of 20 gm.) were given, and 500,000 units were left in the pleural space after each of eight thoracenteses. The empyema decreased in amount and became sterile, but the fever and clinical condition did not improve until about three weeks after the drug was discontinued. The child then became well during the ensuing three months.—*Streptomycin Treatment of Empyema Caused by Hemophilus Influenzae*, A. J. Fisher & E. B. Shaw, *Am. J. Dis. Child.*, October, 1947, 74: 468.—(W. H. Oatway, Jr.)

**Viral Pneumonia.**—*Primary atypical pneumonia* is the term used to signify the type of viral pneumonia which has been prevalent in recent years. The cause has not been definitely established, but it is believed to be a

filter-passing agent, presumably a virus. Pathologic data are relatively meager because the case mortality rate has been so low. An acute bronchiolitis and interstitial pneumonitis have been noted. Pleural surfaces were smooth. The amount of edema or hemorrhage in the parenchyma showed great variation. The microscopic picture was variable. Primary atypical pneumonia appears to be transmitted from man to man by the respiratory route. The incubation period is usually ten to fourteen days with a range of five to twenty-one days. The disease appears to be moderately communicable. Epidemics tend to run a period of many months. All age groups are affected. Sporadic cases occur at frequent intervals in the general population. The duration of immunity following one attack has not been definitely established. The onset is usually gradual. The most common symptoms are fever, chills, cough, malaise and headache. Coryza and sore throat are less common. Chest pain is often noted. Physical examination is usually unremarkable except that the patient appears somewhat ill, the pharynx is often moderately injected, and chest examination often reveals small areas of dullness and subcrepitant râles. The subsequent course is quite variable. Most patients never appear severely ill. For each patient who develops pneumonia, there are three to ten times as many who have the virus infection, but who do not develop pneumonia. Only about one-fifth of the patients with pneumonia become seriously ill, with prolonged fever and extensive pulmonary infiltration. The white blood count is usually within normal limits. Counts exceeding 12,000 are exceptional unless there is a concurrent bacterial infection. As the disease progresses, however, the white count tends to rise. The sedimentation rate is elevated early in the course of the pneumonia and returns gradually to normal. Chest X-ray films reveal areas of increased density compatible with pneumonia. Fifty-six per cent of 801 patients with a clinical diagnosis of primary atypical pneumonia reveal significant titers of cold agglutinins in the convalescent sera. Comparable titers

(40 or over) were found in only 4.4 per cent of 1,719 patients with other diseases, and in 8.1 per cent of 209 normal subjects. The agglutinin titer, in general, begins to rise between the seventh and fourteenth days after onset, reaches a peak about three weeks after onset, and then falls off fairly rapidly. In certain patients titers remain significantly elevated for only a short period. Blood serum had best be examined during the first week of the illness and one or more specimens collected after the twelfth day of the disease. The test has considerable practical value as a means of classifying cases of primary atypical pneumonia. Using the streptococcus MG agglutinins, Horsfall found that 48.9 per cent of 438 cases of primary atypical pneumonia showed titers of 20 or more, while only 5.1 per cent of 349 patients with other diseases and 5.3 per cent of 357 normal subjects showed titers as high as this. In general, patients developing streptococcal agglutinins also develop cold agglutinins, but many patients with the latter do not have the former in significant titer. For this reason the cold agglutination test appears to be more useful for diagnosis. The significance of cold agglutinins and other streptococcal antibodies is not yet clear. *Treatment:* Therapy remains symptomatic. Sulfonamides and penicillin have no definite therapeutic effect. Treatment with convalescent serum has not been proved effective. Codeine is useful for patients with distressing cough. Oxygen may be necessary for severely ill patients. Convalescence may often be long. *Viruses in the psittacosis group:* This virus is present not only in psittacine birds, but also in pigeons, doves, domestic poultry, sea birds, and probably other avian species. The latent virus has been recovered from rodents and cats. The number of human cases of pneumonia caused by psittacine viruses is relatively small. Pneumonia caused by the psittacosis virus is often much more severe than ordinary primary atypical pneumonia. Psittacosis pneumonia may have a case fatality rate of between 20 and 40 per cent. It is important to note that experimentally the psittacosis group of viruses are susceptible to penicillin



and preliminary clinical trials in humans have been definitely encouraging. Clinically the patient is sicker than with a simple pneumonia. The white count is usually low, although considerable variation occurs. X-ray findings are indistinguishable from those seen in other viral pneumonias. Diagnosis can be established by isolation of the agent from sputum or, in early cases, the blood, or by demonstrating a greater than four-fold increase in antibody titer in complement fixation tests with acute and convalescent sera. There is no significant increase in either cold or streptococcus MG agglutinin titer. Treatment should be instituted with penicillin as soon as the diagnosis appears reasonably well founded on clinical grounds since laboratory confirmation cannot be expected at an early date. At least 50,000 units intramuscularly every three hours should be used. *Influenzal pneumonia*: Either type A or type B influenza virus may cause a primary viral pneumonia, or may initiate bacterial or mixed viral and bacterial pneumonia. There is at present no specific treatment for primary influenza viral pneumonia. Secondary bacterial pneumonia responds favorably to sulfonamide or penicillin therapy. *Q fever*: This rickettsia may be responsible for a type of pneumonia virtually indistinguishable from the ordinary viral pneumonia. Clinically the cases are indistinguishable. No specific therapy is available. Diagnosis rests on laboratory means.—*Viral Pneumonia*, G. Meiklejohn, *M. Clin. North America*, November, 1947, 31: 1442.—(B. Hyde)

*Pneumonia of Azygos Lobe*.—A case report of an 18-year-old male with pneumonia of the azygos lobe, which resolved on a full course of sulfadiazine, is presented. Pulmonary tuberculosis, apical segmental consolidation, segmental atelectasis, mediastinal effusion, and mediastinal neoplasm were considered in the differential diagnosis.—*Pneumonia of the Lobe of the Azygos Vein*, T. C. Shuddert & A. K. Turnbull, *Brit. J. Radiol.*, March, 1947, 20: 119.—(B. Hyde)

*Treatment of Pneumonia*.—*Lobar pneumonia*—abrupt onset with chill, fever, cough,

sharp chest pain, dyspnea, rusty or blood-streaked sputum. There may be splinting of the affected side of the chest, pleural friction rub, dullness to percussion and tubular breathing. Chest X-ray reveals a dense, homogeneous shadow. Pneumococci are the causative organisms in 97 per cent of attacks of lobar pneumonia. Sulfadiazine is the sulfonamide of choice in therapy. Dosage may be 4 g. followed by 2 g. in two and four hours, followed by 1.0 g. every four hours day and night until temperature reaches normal and remains there for forty-eight to seventy-two hours. Reactions may occur in 10 per cent of patients. To prevent renal complications, patient should receive 3,000 centimeters of fluids daily; also 2 g. of sodium bicarbonate three times a day. Other toxic reactions are skin reactions, fever and blood changes. Penicillin is effective against pneumococci as well as other gram positive organisms. Dosage may be 20,000 units every three hours of the aqueous solution, or a daily injection of penicillin beeswax and oil, 200,000 to 300,000 units. Penicillin may be given orally, an initial dose of 200,000 units, followed by 100,000 units every three hours. Results of chemotherapy are clear. Before specific therapy, the mortality rate at Cook County Hospital, Chicago, was about 35 per cent (24 to 48 per cent). With chemotherapy, the mortality rate has dropped to 12 per cent (40 per cent of these were patients who were moribund on admission). Anti-pneumococcus serum may be used if sputum pneumococci are typed. It may be used with chemotherapy in cases where the prognosis is dubious. *Atypical pneumonia* occurs more frequently in adolescents and young adults. The lungs may be clear for several days. The leucocyte count tends to be normal. Chest X-ray may reveal only increased hilar markings with possible irregular shadows, or there may be more extensive mottling. A virus origin is likely. There is no specific therapy. Bed-rest and symptomatic care are the rule. Sulfadiazine and penicillin often are used and results may be most gratifying. *Bronchopneumonia* is usually secondary to other infections. It is usually bilateral. Penicillin is usually more effective than sulfadiazine. Ex-

port nursing care is necessary. If the causative organism is the beta hemolytic streptococcus, sulfadiazine should be used, and continued for at least one week of normal temperature. *Aspiration pneumonia*—there is a necrotic as well as an infectious process present. The cough reflex is diminished or absent. This may occur in coma and the symptoms may be profound. Prophylaxis is important since the prognosis is grave. Penicillin is used for therapy. *Friedländer pneumonia* may be lobar or lobular. Sulfadiazine and streptomycin are most effective in treatment.—*The Treatment of Pneumonia*, F. B. Kelly, M. Clin. North America, January, 1947, 31: 52.—(L. Hyde)

**Penicillin for Juvenile Respiratory Infections.**—One hundred and forty-three infants and children with acute respiratory infections, and with fevers of at least 100° F. on admission to the hospital, were given penicillin by mouth. The drug was crystalline type G, unbuffered. The dosage was varied according to age, but averaged 3,000 U. per kilogram body weight, and was given every three hours. The blood levels were satisfactory and well maintained in children from one to 12 years of age; they were higher in infants of less than one year. Two-thirds showed good results, i.e., subsidence of fever and clinical improvement within forty-eight hours. A virus component was probably present in many cases. Evaluation on the basis of cultures or blood counts changed the results only slightly. The method is considered to be valuable.—*The Treatment of Acute Respiratory Infections in Children with Orally Administered Unbuffered Penicillin Solutions*, W. S. Hoffman, J. W. Hofer & H. Gordon, J. Pediat., January, 1948, 32: 1.—(W. H. Oatway, Jr.)

**Inhalation of Penicillin Dust.**—The principle utilized in this newer method is based on the negative pressure created during normal inspiration. It is felt that inhaling penicillin dust in this manner is more physiological and permits a more even and perhaps wider distribution of medicament throughout the respiratory tract than by the use of solution nebulized by oxygen pressure. The patient is

not required to manipulate an exhaling valve during the expiratory phase, the cumbersome equipment of oxygen tank and gauge is not necessary and the preparation of solutions is obviated. The inhalation of the dust particles yields a greater effect than the vapor because of the increased concentration of penicillin per unit area and because of the localized absorption of the penicillin where it comes in contact with the mucous membranes. The authors used crystalline sodium penicillin processed to #50–100 mesh particles and present details of an oronasal mask similar to the simple respirator used by spray painters. All patients received 100,000 units of penicillin dust by inhalation for twenty minutes three times a day. No sensitivity reactions were noted in 68 patients whose diagnoses varied from common colds to bronchiectasis. Blood level curves indicated a slow absorption, the maximum level being obtained about three hours after inhalation. Clinical improvement was noted much more quickly than had been observed previously in a similar group of patients with penicillin aerosol, and fewer treatments were necessary for maximum benefit.—*Inhalation of Penicillin Dust*, L. Krasno, M. Karp & P. S. Rhodes, Science, September 12, 1947, 106: 249.—(E. A. Rouff)

**Intrabronchial Penicillin in Suppurative Disease.**—The authors decided to treat cases of bronchopulmonary suppuration by direct instillation of penicillin. They used the same catheters as for bronchography. A total of 63 patients were treated. Accurate localization of the lesions is necessary. Following local anesthesia, the catheter was directed toward the bronchus of the diseased segment. The patient was then placed in such a position that the end of the catheter was vertically above the affected segment. A solution of 100,000 units of penicillin in 5 to 10 cc. of saline was injected slowly. The patient remained in position for thirty minutes. The treatment was repeated every two days. The average number of treatments was 8. There was no selection of cases. In those with underlying disease such as bronchiectasis or neoplasm, there was no definitive cure but considerable

relief of symptoms was obtained. In cases of lung abscess, there was complete recovery in 17, good clinical results without cure in 6 and failures in 5 cases. Four patients with suppurative bronchitis were improved. The amount of sputum decreases after the first installation and almost disappears after the second. Simultaneously, there is a drop in fever and the patient begins to gain weight.—*Treatment of Broncho-Pulmonary Suppuration by Local Injection of Penicillin*, H. Metrás & J. Lieutier, *Thorax*, December, 1947, 2: 196.—(A. G. Cohen)

#### Aerosol Penicillin in Respiratory Disease.—

A nebulizer must deliver particles of 5 microns in diameter or less in order to be of value in respiratory disease. A test of suitability can be made with 5 per cent glycerine which should give a fine smoke which floats in the air. In this study, 34 subjects were treated with aerosols of Zephiran (alkyl dimethyl benzyl ammonium chloride) in aqueous solution; this is a detergent. Use of detergents is advantageous in the treatment of sheltered foci since the activity of both penicillin and streptomycin is enhanced by their use. Originally an initial dose of 50,000 units of penicillin was injected intramuscularly followed by 10,000 units every three hours for ten days. Later daily injections of penicillin in beeswax were substituted. Immediately prior to treatment, 0.5 cc. of a 0.25 per cent solution of neosynephrine was administered through the nebulizer. This was followed by administration of 100,000 units of penicillin in 3 cc. of Zephiran in a 1:1000 aqueous solution. This was repeated every eight hours for ten days, during which time the patient remained in the hospital. Of 21 patients with bronchiectasis, 10 were improved, 6 were improved temporarily but relapsed and 5 were not helped. Of 12 patients with chronic bronchitis, 8 were improved, 1 relapsed after temporary improvement and 1 was not relieved. In 2 patients with pneumoconiosis, there was definite benefit in that respiratory deficiency was relieved. Good results were obtained in one case of severe asthma and in improving the

secondary infection in 2 cases of tuberculosis.—*Aerosol Therapy of Respiratory Disease*, V. Bryson & E. J. Grace, *New England J. Med.*, November 6, 1947, 237: 683.—(A. G. Cohen)

**Intrabronchial Penicillin in Lung Abscess.—**Eleven cases of lung abscess were treated by intrabronchial instillation of penicillin. Treatment was given every two to three days for a total of three to eight days. On the other days, nebulized penicillin was administered. Of the 11 cases, 10 were cured.—*Intrabronchial Penicillin for Lung Abscess*, E. Rosenthal, *Lancet*, December 6, 1947, 2: 829.—(A. G. Cohen)

**Penicillin in Chest Surgery.—**A study has been made of the levels of penicillin in the blood serum after administration by various portals, and of levels in the pleural fluid after intramuscular injection. The intramuscular route is the most efficient in producing and maintaining blood levels, and it results in satisfactory levels in the pleural fluid; 40,000 units is a better dose than 20,000. Direct intra-pleural instillation produces high and prolonged local concentrations, with some absorption; it is recommended when aspirations are being done, or for postoperative inclusion. Inhalation of an aerosol obviates the use of hypodermic injections, but requires cooperation of the patient, wastes drug in producing suitable blood levels, and is inferior to intratracheal instillation for the latter effect. It should only be used, with these limitations in mind, for the temporary reduction of the Gram positive coccil flora. It is not a panacea, but does have satisfactory local efficiency; direct nebulization was superior to the use of a BLB mask.—*An Evaluation of Methods of Penicillin Therapy in Thoracic Surgery*, J. H. Donnelly, F. J. Phillips, J. T. Bartlett, & W. E. Adams, *Ann. Surg.*, October, 1947, 126: 579.—(W. H. Oatway, Jr.)

**Amebic Lung Abscess.—**Amoebiasis is endemic in Argentina, where 20 to 30 per cent of the population is infected. Amebic lung abscess is rare and very often mistaken for tuber-

culosis, cancer or mycotic disease. The purpose of this paper is to facilitate the early diagnosis of this condition. Only occasionally is amebic lung abscess due to lymphatic or hematogenous spread. Generally, it is a direct extension from liver abscesses. First, there is hepato-pleural irritation with all the symptoms of a subphrenic abscess. After invasion of the lung, profuse sweating, tachycardia and cyanosis with the clinical findings of pneumonitis or atelectasis set in and may be mistaken for a fulminating tuberculosis of the right lower lobe. There may be temporary improvement until repeated disseminations of amebae cause severe broncho-pleuro-pulmonary irritation with persistent asthma-like dyspnea. Finally, the abscess breaks and opens into a bronchus, the mediastinum or pericardium, sometimes into the peritoneal cavity or through the chest wall. Most common is the bronchial perforation which causes sudden vomica of great quantities of odorless chocolate colored matter. This is the most important differentiation from lung abscess. The sputum may be sterile or it may contain any one of the pyogenic bacteria. Only occasionally, amebic cysts can be found. Inoculation of the sputum into the rectum of young cats may help to establish the diagnosis. In cases of proved intestinal amebiasis with negative findings for acid-fast bacilli the possibility of amebic lung abscess should be considered. However, the coexistence of tuberculosis is not uncommon. Bronchoscopy and bronchography should be done to rule out cancer. Exploratory thoracotomy is a potential means for spreading infection to the chest wall, as is diagnostic pneumothorax. All cases of amebic lung abscess show a partial or complete paralysis of the hemidiaphragm. A freely movable diaphragm is proof that there is no involvement of pleura or lungs. Lung cancer in its early stages is associated with severe pain, whereas the pain in pulmonary amebiasis is only slight. The differential diagnosis from hydatid cyst is very difficult and has sometimes to rely upon biological tests only. Tuberculosis of the right lower lobe must be ruled out by history of contact and the tuber-

culin reaction. In the X-ray the abscess is surrounded by a zone of inflammatory reaction. For the treatment of amebic lung abscess emetine is the specific drug. The history of a significant case is given.—*Abscesco amibiano de pulmon, M. Schneider, Arch. argent. de tisiol., 1946, 22: 42.*—(W. Swienty)

**Pulmonary Infarction in Children.**—Only about 100 cases have been referred to in the literature since 1833. The condition is probably unrecognized at times, since the present report from the Mayo Clinic includes 38 new cases. Embolism and thrombosis in the lung are the causes of infarction. It is difficult to distinguish between the two, but embolism probably occurs with slightly greater frequency. A local pathological change in the lung is usually required to produce the infarction. The usual factors in thrombosis are endothelial injury, circulatory stasis, and changes in the blood; the contributing causes may be infection, atelectasis, allergy, and venoclasia. In 24 of the 75 cases previously described in detail, thrombi were noted elsewhere in the body. Pulmonary and general symptoms occur following the occlusion of a pulmonary artery, the intensity depending upon the speed of obstruction. Death may be due to the mechanical changes and/or reflex factors. A diagnosis of infarction during life is rare. A sudden onset of shock with cardio-respiratory embarrassment is suggestive, but the onset may be slow, with intra-bronchial symptoms similar to those of pneumonia. In the differential diagnosis pneumonia and atelectasis must be considered. X-ray signs become visible in twelve to twenty-four hours. In the current series of 38 cases, only 3 were diagnosed clinically. The condition followed surgery in 42 per cent of the cases, a lung infection was present in 34.2 per cent, and some sort of infection was present in the body in 84.2 per cent. Children with a background similar to that which has been described should be observed closely for evidence of peripheral thrombosis; the onset of suggestive symptoms may then lead to the diagnosis.—*Infarction of the Lung in Children, E. Zuschlag, Am.*

*J. Dis. Child.*, October, 1947, 74: 399.—(W. H. Oatway, Jr.)

**Hemopneumothorax in Infarction of Pulmonary Lobe.**—A case is reported of a 39-year-old colored male who developed complete infarction of the lower lobe of the left lung subsequent to long continued passive congestion. The infarction underwent rapid aseptic softening with consequent rupture into the pleural sac, producing hemopneumothorax. A search of the available literature has revealed only 5 such cases, in only 3 of which the lesion was proved by postmortem examination. To this small series the authors add a sixth case, which shows several unusual features, namely: the large size of the pulmonary infarction, the aseptic character of the softening, its rupture into the pleural cavity with the causation of hemopneumothorax, jaundice and a high blood urea nitrogen. An analysis of dates on reported cases is also given.—*Infarction of an Entire Pulmonary Lobe with Subsequent Aseptic Softening Causing Sterile Hemopneumothorax*, A. J. Rawson & J. A. Cocke, *Am. J. M. Sc.*, November, 1947, 214: 520.—(G. F. Mitchell)

**Progressive Coccidioidomycosis.**—A 24-year-old male developed headache, fatigue and fever two weeks after he had made two trips to the San Joaquin valley. Chest X-rays, at first negative, later showed pulmonary and pleural involvement on the left. Coccidioidin skin tests were positive at the onset; later, they became negative. Complement fixation tests for coccidioides immitis remained positive at 1:8 dilution throughout. Gastric lavage specimens and pleural fluid were negative for bacteria and fungi. Penicillin therapy was ineffective in doses of 60,000 units every three hours. The course was downhill and the patient died in coma about five months after onset of symptoms. Postmortem examination revealed extensive caseous and fibrotic involvement of the lungs and pleura. There was also a generalized peritonitis. The brain revealed edema, hyperemia and focal degeneration. Microscopic examination revealed

numerous coccidioides immitis organisms in the lungs, tracheobronchial lymph nodes, liver and kidneys. Most of the organisms were in the spherule stage; a few were enlarged and showed endospore formation. This patient illustrated how short a contact with infected dust can give rise to the disseminated disease. Stabilization of antibody formation as manifested in the complement fixation tests in this case is usually regarded as an indication that the infection is being adequately controlled. In the later course of the disease in this patient, the tuberculin test was positive and the coccidioidin test negative; this combination can be misinterpreted as evidence of active tuberculosis. The pathological findings indicated lymphatic and hematogenous dissemination similar to that occurring in disseminated tuberculosis.—*Progressive Coccidioidomycosis: Report of a Case*, N. A. Harvey, *Ann. Int. Med.*, March, 1948, 28: 651.—(H. R. Nayer)

**Nocardiosis.**—A routine chest film of a 26-year-old physician revealed a minimal infiltration in the right apex. On one occasion a questionable positive sputum was reported. The lesion increased in size and pneumothorax was instituted. A transient pulmonary infiltration was treated with penicillin. The patient developed a right pleural effusion; the fluid was clear and negative for tubercle bacilli on culture and guinea pig inoculation. After several weeks purulent material was aspirated; this revealed numerous colonies of *Nocardia asteroides* in pure culture. In spite of treatment with streptomycin and penicillin the pleural fluid continued to show *N. asteroides*. Marked sensitivity of the organism to sulfadiazine could be demonstrated. The patient received 75 g. of sulfadiazine intrapleurally and 1,268 g. orally. The pleural effusion became sterile and was gradually absorbed. The patient recovered completely and has remained well during a period of observation of fourteen months.—*Nocardiosis, Nocardia Asteroides Infection Simulating Pulmonary Tuberculosis*, R. P. Glorier, W. E. Herrell, F. R. Heilman & K. H. Pfuetz, *J. A. M. A.*, January 17, 1948, 136: 172.—(H. Abeles)

**Pulmonary Aspergillosis.**—The histories of 2 patients are reported. The first patient had been treated for tuberculosis on the basis of numerous hemoptyses and pulmonary infiltrates below the left clavicle; tubercle bacilli were never demonstrated. Left upper lobectomy was carried out. The lesion was found to be a bronchiectatic cyst filled with material in which was demonstrated mycelia and spores of a fungus resembling aspergillus. Presenting symptoms of the second patient were hemoptyses and generalized macular rash. Roentgenograms revealed infiltrations in both hilar areas extending paravertebrally to both apices; later, an effusion appeared at the right base. Penicillin therapy was ineffective and this patient died one month after admission. Postmortem examination revealed considerable interstitial and parenchymatous involvement of the lung with occlusion of many pulmonary vessels and resulting tissue necrosis. Numerous fungi, identified by culture as *Aspergillus fumigatus* Fresenius, were found in the lungs and skin lesions. Numerous granulomatous lesions were seen in the liver and spleen. Sections of the sternum revealed almost complete aplasia of the marrow; this finding has not been previously reported as a complication of aspergillosis. The unrestricted spread of the disease in the second case contrasts with the localized process in the first patient.—*Pulmonary Aspergillosis: Report of Two Cases*, B. Gerstl, W. H. Weidman & A. V. Neumann, *Ann. Int. Med.*, March, 1948, 28: 662.—(H. R. Nayer)

**Aspergillosis.**—Pulmonary aspergillosis occurs in farmers, feed mill workers, fur cleaners utilizing rye flour for removal of grease, threshers and others who have contact with birds or grains. The present case history deals with a child in whom, at the age of two years, a chest roentgenogram showed bronchopneumonia. At the age of 2.5 years and again at 4 years an inflammatory consolidation of the right lower lobe was found. A fluctuant mass developed at the lower costal margin in the left anterior axillary line. Culture of pus aspirated from that lesion revealed *A.*

*fumigatus*. When the child was 5 years old pneumonia of the left lower lobe was found. Laboratory studies were noncontributory. At the age of 7.5 years the child developed pneumonia in both lower lobes and a cerebellar abscess from which *A. fumigatus* was cultured. The child died at the age of 8. Abscesses were found in the brain, dura, heart, lungs, mediastinum, lymph nodes, spleen, liver, right kidney and right ankle. Cultures from various sites revealed *A. fumigatus*. A hematogenous dissemination of the organism is likely.—*Aspergillosis and the Aspergilli: Report of a Unique Case of the Disease*, E. P. Cawley, *Arch. Int. Med.*, October, 1947, 80: 423.—(G. C. Leiner)

**Bronchiectasis.**—Of 400 cases of bronchiectasis, 59 per cent were found unsuited for surgery because of too much or too little disease, lack of symptoms, limited cardiovascular reserve, advanced emphysema, concurrent disease or refusal by the patient. Much can be done for these patients with medical care. This is considered under the following headings: mechanical drainage, control of infection, improvement of general health and prevention. Mechanical drainage requires a suitable position. The head and thorax must extend vertically downward from a high bed or table. Secretions should be thinned out by use of steam, ammonium chloride and creosote. Depressants should be avoided. Bronchodilators should be inhaled through nebulizers. Deep expiratory and inspiratory breathing should be practiced before and during postural drainage. Drainage should be performed often enough to keep the passages empty. Bronchoscopic drainage is not indicated as a routine measure. For control of infection, aerosol and intramuscular penicillin are recommended. These are of value particularly at the beginning of an upper respiratory infection. Treatment of sinusitis also is important. Improvement of general health consists of protection against upper respiratory infections, treatment of anemia, avoidance of cold and wetness, elimination of smoking and change of climate. Prevention consists of early diagnosis and

treatment of bacterial pneumonias and re-expansion of resultant atelectatic lung tissue, especially in children; this is accomplished by deep breathing exercises.—*Bronchiectasis: Treatment and Prevention*, T. L. Badger, *New England J. Med.*, December 18, 1947, 237: 937.—(A. G. Cohen)

**Pathogenesis of Bronchiectasis.**—Any theory of the pathogenesis of bronchiectasis must explain four features: (1) The disease is rarely diffuse. (2) It is usually not progressive and rarely spreads. (3) It is rarely an isolated finding in an otherwise normal lung; the surrounding pulmonary parenchyma is abnormal. (4) It is characteristically a disease of youth. The incidence of the following features in the specimen of a series of 50 lobectomies for bronchiectasis was tabulated: chronic bronchial inflammation, congenital abnormalities, bronchostenosis, atelectasis and pneumonia or pneumonitis. Bronchostenosis and congenital abnormalities were found to be unimportant except in a few cases. The other three factors were each present in more than 80 per cent of cases, but no factor was constant and none was ever a solitary finding unassociated with at least one other factor. The author concludes that bronchiectasis is an acquired disease of the pulmonary parenchyma and the bronchial tree. Parenchymal involvement varies in detail but one feature is common to all cases, namely, reduction in the number of aereated alveoli, a condition which may or may not be reversible. This results in a low intrathoracic pressure which is a very effective bronchodilating force. The assumption of a primary bronchial infection with secondary atelectasis or pneumonitis fulfills the four criteria. In actual experience, bronchial obstruction causes atelectasis by obstructive secretion. This is especially true in infants and children.—*The Pathogenesis of Bronchiectasis*, T. B. Mallory, *New England J. Med.*, November 22, 1947, 237: 795.—(A. G. Cohen)

**Hemangioma of the Lung.**—Visceral hemangiomas are uncommon, and their occurrence

in the lung is very rare. Less than 20 pulmonary cases have been reported, half of these since the definitive description in 1938 by Rodes of cavernous hemangioma of the lung as a clinical entity. A year later the first antemortem diagnosis was made. Probably all cases are congenital, several have been multiple, and physiologically they are arteriovenous fistulas. Perhaps in some cases the shunt enlarges with age, with a resultant late development of cyanosis, though some cases are cyanotic from birth. Typical symptoms, signs, and blood changes are described. A late inspiratory, continuous murmur may be heard over the lesion; clubbing of the digits is a common sign. The X-ray films show non-progressive, cylindrical masses, bronchograms are negative, and pulsations are seen fluoroscopically. In six previous cases which have been operated on excision of a part or all of the lung has been curative. The case of a 29 year old male is reported. Symptoms had been present for eight years, following a pneumonia, cyanosis had been noted for six years, and the condition gradually became debilitating. X-ray and laboratory findings were typical. A successful lobectomy was done, the lesion was demonstrated in an angiogram of the specimen, and the patient is well several months after surgery.—*Pulmonary Cavernous Hemangioma with Arteriovenous Fistula, Surgical Management*, J. D. Bisgard, *Ann. Surg.*, December, 1947, 126: 965.—(W. H. Oatway, Jr.)

**Bronchotomy for Bronchial Tumors.**—In order to avoid resection of healthy lung tissue, bronchotomy is recommended for the removal of benign bronchial tumors in selected cases. These are cases in which there has been a relatively rapid development of obstructive symptoms, and in which there appears to be relatively little pulmonary infection. The surgical hazards are reviewed and the technique is discussed. The procedure was carried out in one case, with an excellent result.—*The Indication for Posterior Transpleural Bronchotomy in the Management of Intrabronchial Tumors*, H. T. Langston &



*R. T. Fox, Surg., Gynec. & Obst., February, 1948, 86: 192.—(A. G. Cohen)*

#### Pulmonary Disease in Beryllium Workers.

—The late Dr. Leroy Gardner was intensely interested in the problem of detecting the agent responsible for the lung lesions in patients who had been exposed to beryllium compounds in the form of dust. While he was not prepared actually to condemn beryllium, he definitely felt that it was involved in some as yet unrecognized way. It was at his suggestion that the roentgen study of the chest films of 32 patients, exposed to beryllium dust and in whom delayed pulmonary changes occurred, is presented. The majority of the patients were females having an average exposure of sixteen months. An average of twenty-months transpired after the period of exposure before symptoms of the first X-ray evidence were discovered. The physical findings were limited to impaired resonance and fine râles throughout the lungs. Cyanosis was present in several cases. The laboratory findings were meagre, polycythemia being the only constant factor. Ventilation function tests revealed respiratory disability. The clinical course was variable. Some patients died after an illness of two years; many improved and were able to work though they were not symptom-free. Pathological study showed a granulomatous reaction infiltrating or completely obliterating the interstitial tissue as the predominant lesion. The mediastinal nodes were similarly involved. Four patients were thoroughly investigated and their histories are presented. The roentgen findings are limited to the lungs and are characterized by a bilateral uniformly widespread diffusely granular or "sandpaper" appearance and/or nodular infiltration. No definite disease entity is known which can produce the fine disseminated granular type of infiltration observed in these cases. In both types, but more so in the granular, coalescent or confluent shadows may develop which are more noticeable in the middle third of the lung fields. A reticular pattern may also be seen on stereoscopic examination in the granular type. The

apices and costophrenic sulci were generally free. Vascular markings are obscured except at the base and in advanced cases may be obliterated. No valid correlation between the clinical course of the disease and the magnitude of the pulmonary changes could be made. The final result also is not known in those patients with clinical remission but persistent lung lesions. The prognosis should be guarded in patients with the granular type of nodulation, especially when confluent shadows are superimposed. It is also emphasized that roentgen changes may exist with insignificant or no symptomatology. Roentgen differential diagnosis may be difficult. Many of the patients were at first suspected of having Boeck's sarcoid, while a diagnosis of silicosis was almost as frequently entertained. Other pulmonary diseases that enter into consideration are chemical pneumonitis, tuberculosis, bronchomycoses, cardio-vascular disease, miliary carcinosis and erythema nodosum. It is possible that a serious type of pneumoconiosis not heretofore described is being dealt with.—*Pulmonary Disease in Workers Exposed to Beryllium Compounds: Its Roentgen Characteristics, L. M. Pascucci, Radiology, January, 1948, 50: 23.—(G. F. Mitchell)*

**Bagassosis.**—Bagasse disease of the lungs, or bagassosis, is a pulmonary disorder brought about by the inhalation of dried bagasse dust. Only 30 or 40 cases have been reported. Most cases reported are from localized communities where the fibers of bagasse are processed into the manufacture of acoustical and thermal insulating building materials and refractory brick, or where the sugar cane is grown. The same characteristics for the disease are reported in all places. About two months' exposure to the dust are required before symptoms appear, although the time has varied from three weeks to two years. The disease manifests itself as an acute febrile illness with extreme shortness of breath, a persistent cough with scanty mucoid sputum and a profound weakness. The onset is insidious and gradual, the patients usually not realizing that they are ill until they are seized by a sudden cough-



ing spell and become so dyspneic as to be forced to rest. Patients with a long exposure to heavy concentrations of the dust become critically ill and appear to have a severe bronchiolitis and pneumonia. A mortality rate of 8.3 per cent was reported in 24 cases collected, which indicates that this is an industrial disease of a serious nature. In cases having a short exposure, the disease usually clears up in two to six months. In view of the obscurity of the exact etiology of bagassosis, there is no specific treatment. Most of the patients have been treated symptomatically. There is no notable response among those in whom the sulfonamides were tried, or in the one case treated by penicillin. Oxygen has afforded some relief of the dyspnea in the more serious cases. The pulmonary changes incited by inhalation of bagasse dust consist of diffuse infiltration and consolidation and an acute bronchiolitis or pneumonia similar to that seen in pneumoconiosis. However, in one respect it differs markedly; this is a reversible reaction with resolution and the lung regains its normal appearance on the roentgenogram. Three cases of bagassosis are reported, including a discussion of the symptoms, the physical and laboratory findings, and the clinical course.—*Bagasse Disease of the Lungs*, D. V. LeMone, W. G. Scott, S. Moore & A. L. Koven, *Radiology*, November, 1947, 49: 556.—(G. F. Mitchell)

**Pulmonary Hemosiderosis.**—The literature contains reports of 17 cases, all but one of which terminated fatally. All but one were children who ranged in age from a few months to 16 years. The condition is characterized by recurrent attacks, often sudden in onset, of fatigue, cyanosis, pallor, increasing dyspnea and acceleration of pulse rate. There is a troublesome cough often followed by vomiting. At times there is blood in the sputum or vomitus. There may be abdominal pain. The temperature at the height of an attack may reach 103° F. Severe attacks can be very alarming. The patient is restless and often apprehensive. Each attack lasts two to three days. Toward the termination, the patient shows pallor and often jaundice. There is in-

creased liver dulness and the spleen is palpable; there is often clubbing of the fingers. The attack begins with tachycardia, followed in twelve to twenty-four hours by dyspnea, pallor and fever, with or without jaundice. The clinical picture is one of congestive cardiac failure, especially of the lesser circulation. Recovery often is rapid but during intervals there is debility, undernutrition and dyspnea upon exertion. The diagnosis of hemolytic jaundice often is made. The true nature of the condition is unnoticed unless the chest is X-rayed. Between attacks, the pulmonary physical signs are insignificant; there may be a few scattered rhonchi. X-rays show mottled shadows which are most noticeable in the hilar areas. There is diffuse speckling throughout the lung fields. The abnormal shadows are accentuated during the attacks. There is often evidence of a partial lobar collapse. The shadows resemble those of miliary tuberculosis, except that, instead of dots, there are small, clear circular spaces surrounded by thickened opaque walls, giving a pumice-stone appearance. There is a good deal of similarity to the picture of sarcoidosis or Gaucher's disease. The cardiac shadow is enlarged to the right and the pulmonary conus is prominent. Examination of the blood shows a severe type of secondary hypochromic anemia with high reticulocytosis. Of the 17 previously reported cases, 5 were male and 10 female. The onset occurred in infancy or early childhood. There was no familial relationship among patients. All but one patient died with signs of left heart failure after several years of ill health. At autopsy, the main lesions are found in the lungs. Macroscopically, these are full and firm, of a dark reddish-brown color, with fine hemorrhages visible on the pleural surfaces. On section, there is pneumonic hepatization with a dark red-brown color of the cut surfaces. Enlargement of the tracheobronchial lymph nodes is conspicuous. The heart is enlarged, especially on the right side. Microscopically the alveoli in large areas are crowded with hemosiderin-laden phagocytes. The epithelial cells of the alveolar walls also contain hemosiderin; many are desquamated within

the alveoli, which also contain red cells and hemosiderin granules lying free. There is considerable thickening of the alveolar walls and interlobular and peribronchial tissues. Hemosiderin granules are contained within the interstitial tissues and also the nodes. The present series consists of 7 cases, 2 male and 5 female. The oldest was 13 years of age. No consanguinity was evident. Two patients have died. Of the 5 who are living, 3 are still subject to attacks. Tabulation of the clinical features shows hemoptysis or hematemesis in 6, positive chest X-ray findings in 7, palpable spleen in 3 and cardiac enlargement in 4 cases. Blood studies show hypochromia and increased reticulocytes; white blood and differential counts, platelets, clotting and bleeding times and red cell fragility all are normal. The anemia tends to subside in remissions, especially if the patient is given iron. Certain features such as reticulocytosis, nucleated red cells, slight jaundice, indirect van den Bergh reaction and slight increase in urinary urobilinogen suggest hemolytic anemia. But all these findings can be explained by the recurrent pulmonary hemorrhages with subsequent hemolysis. Histologically, even the youngest cases show evidence of capillary stasis and aggregation of heart failure cells and fresh red cells in the alveolar spaces. There is progressive thickening of the fibromuscular elements in the alveolar septa. Giant cells appear, which engulf the elastic fragments, and travel to the lymph nodes. The interalveolar capillaries become dilated and tortuous. Changes also appear in the small and medium-sized vessels. The bronchi are normal. The increase of reticulin, collagen and muscle and the decrease of elastic fibers results in a lack of distensibility of lungs, with consequent peripheral stasis in the capillary bed. This is followed by diapedesis and deposition of hemosiderin. Changes are slight at first. Gradually, larger portions of the lungs become involved. This explains the periodic course and increasing severity with eventual anoxemia. The hemosiderin deposits, fibrosis and collapse form the pathological basis for the radiological appearance. Pulmonary hemosiderosis had no rela-

tionship to generalized hemosiderosis and hemochromatosis. There is no disturbance in iron metabolism.—*Idiopathic Pulmonary Hemosiderosis*, W. G. Wyllie, W. Sheldon, M. Bodian & A. Barlow, *Quart. J. Med.*, January, 1948, 17: 25.—(A. G. Cohen)

**Mediastinal Emphysema.**—From March 15, 1943 to March 15, 1947, at the University of Wisconsin, the author observed 6 students with spontaneous pneumothorax without recognized mediastinal emphysema, 7 with pneumomediastinum without recognized pneumothorax and 7 with both conditions. Spontaneous mediastinal emphysema occurs when air from a ruptured alveolus dissects along the perivascular sheaths to the mediastinum. Associated pneumothorax may be caused by rupture of the mediastinal air through the mediastinal pleura. It is probable that this mechanism operates in the majority of cases of spontaneous pneumothorax in otherwise healthy individuals; the initial pneumomediastinum may be transient or unrecognized. In mediastinal emphysema there is a characteristic sudden onset of pain, usually substernal and associated with change in position. The case histories of 14 cases of mediastinal emphysema are summarized. Six were aware of peculiar sounds over the precordium. A crunching sound synchronous with the heart beat is pathognomonic. Hyperresonance over the precordium was a constant finding in the author's series. In 3 patients, mediastinal air was demonstrated either by X-ray or fluoroscope. Electrocardiograms revealed no characteristic pattern. There was no significant change in leucocyte count or sedimentation rate. The occurrence of pneumothorax does not alter the course of mediastinal emphysema. Four of the 20 patients were tuberculin-positive. No student showed any lesions regarded as tuberculous in nature. Hospitalization of patients with spontaneous pneumothorax was advised only when seen early or when definite symptoms were present. Aspiration of air was carried out only for dyspnea or, in large collections, to hasten expansion of the collapsed lung. Prophylactic use of

sulfonamides or antibiotics is not recommended.—*Spontaneous Mediastinal Emphysema and Spontaneous Pneumothorax—A Report of 20 Cases, Helen A. Dickie, Ann. Int. Med., March, 1948, 28: 618.*—(H. R. Nayer)

**Bronchial Asthma.**—In view of the conflicting and incomplete statements in the literature concerning pulmonary ventilation, oxygen consumption and blood pressure values in bronchial asthma, this study was made to find out whether the results previously obtained by the author in experimentally induced asthma in guinea pigs could be verified in tests on asthmatic patients during and after the attack. The effect of the antiasthmatic drugs used in this investigation were studied on healthy persons, as well as on asthmatics during asthma-free periods and taken into account. It was found that, in accordance with the animal experiments, the pulmonary ventilation and oxygen consumption during severe attacks are lower than under normal conditions. Thus, an oxygen deficit occurs and this is made up by a considerable increase in the oxygen intake after the attack. In mild attacks, ventilation and oxygen intake are considerably greater than normal, the increment in the latter being as great as 100 per cent. In severe attacks, the systolic and diastolic blood pressures are considerably increased (the latter not constantly); in mild attacks, there is either insignificant or no increase. The altered gaseous tension seems to bring about changes in the intermediate metabolism probably affecting the condition of the patient. The author has previously demonstrated in guinea pigs that such insufficient metabolism causes a decrease in tissue reparation; this results from the break-down of co-enzyme and co-phosphorylase.—*H. Colldahl, On the Pathophysiological and Clinical Aspects of the Crises of Asthma Bronchiale, I., The Pulmonary Ventilation, Oxygen Uptake and Blood Pressure, Act. Med. Scand., Sept., 1947, 128: 551.*—(O. Pinner)

**Bronchial Asthma.**—Temperature studies show that in severe attacks of bronchial

asthma the temperature of the body falls, while in mild attacks a rise occurs. These changes are the same as previously found by the author in experimentally induced asthma in guinea pigs. However, in asthmatic patients it is difficult to decide what the influence of the concurrent bronchitis may be. Especially, retention of bronchial secretion may bring about temperature elevation. But the decline of the temperature during severe attacks cannot be due to infection, and the assumption that elevation in mild attacks is always a toxic manifestation of bronchitis is contradicted by the fact that in certain cases the temperature rises simultaneously with the transition of severe to mild asthmatic symptoms. The toxic influence of a bronchitis on the heat-regulating centers should be strongest at a time when the asthma attack is most severe and the sputum is tenacious and small in amount, but not when the attack and sputum retention are subsiding. Finally, the similarity of the temperature curves in experimental and in bronchial asthma argues against the theory of an infectious cause of the temperature rise. All this indicates rather that the asthmatic breathing as such has a decisive influence on the temperature. The mechanism involved, arising from the peculiarities of ventilation and oxygen consumption in mild and severe asthma, respectively, is analyzed in this paper. Asthma with an irregular course and with alternating mild and severe attacks shows an irregular temperature curve. A moderate rise in temperature of an asthmatic patient must, therefore, not be interpreted in all cases as due to infection.—*On the Pathological and Clinical Aspects of the Crises of Asthma Bronchiale, II, Effects of the Crises on the Body Temperature, Helge Colldahl, Act. Med. Scand., Oct., 1947, 129: 19.*—(O. Pinner)

**Tuberculin Sensitivity.**—The object of this study was to determine the relationship, if any, between the size of the tuberculin reaction and the presence and degree of tuberculous infection. Old Tuberculin in doses of 0.05 mg. and (if negative) 1.0 mg. were injected intracutaneously; the reactions were

interpreted in 48 to 72 hours. A total of 610 persons over the age of 15 were tested; this number included both healthy persons (contacts, etc.) and clinical cases. The size of the reaction was graded. Among nontuberculous individuals, the most intense reactions were noted in persons who were contacts with open cases. Milder reactions were found in both noncontacts or contacts with negative cases. The least intense reactions were seen in noncontacts. As the cases were followed, the strong reactions tended to grow milder. Increased sensitivity was found in cases with erythema nodosum and in primary tuberculosis, especially during the early phases. In clinical pulmonary tuberculosis, the reaction was greater in the exudative than in the productive type. It gradually decreased to a constant point. In healed cases, a new exposure often resulted in an increased reaction without the appearance of new lesions. In cavitory tuberculosis, the sensitivity was low.—*Significance of Tuberculin Sensitivity*, I. Bluhm; *Tubercle*, April, 1948, 29: 73.—(A. G. Cohen)

**Chemotherapy of Tuberculosis.**—L-rhodinic acid and d-citronellie acid and the hydrogenated product of l-rhodinic acid, i.e., 1-dihydro-rhodinic acid, were applied by mouth to 68 patients suffering from advanced pulmonary tuberculosis. Their course before and after the application was observed, as well as the fluctuation of tubercle bacilli in sputum. Data on 28 cases among the 68 patients are shown. The chief clinical phenomena which appeared on applying these fatty acids were: diminution or even disappearance of tubercle bacilli in sputum, regression of exudative lesions as shown by X-ray films, and sometimes disappearance of cavities, and decrease in sedimentation rate.—*Ueber die chemotherapeutische Anwendung von 1-Rhodinsäure, einem Bestandteil des Oels des Taiwankhinoki-Baums, und von einigen naheverwandten Fettsäuren bei tuberkulösen Patienten*, S. Katsura, T. Nozoe & co-workers, *J. Med. A. Formosa*, 1941, 40: 1557.—(E. R. Long)

**Chemotherapy of Tuberculosis.**—Investigations on the treatment of pulmonary tuberculosis with certain fatty acids were extended. Longer follow-up studies were carried out and, in addition to l-rhodinic and d-citronellie acid, geranic acid and its hydrogenated products, dihydro-geranic acid (dl-dihydro-geranic acid) and tetrahydro-geranic acid, were tested. The results were qualitatively similar to those of the former report. Tubercle bacilli disappeared in 40 of 193 (20.7 per cent) cases. They disappeared more frequently in cases with comparatively small changes than in those with large changes, e.g. they disappeared in 21 out of 45 (46.7 per cent) cases without cavity images, in 29 out of 70 (41.4 per cent) cases with changes in localized fields, and in 15 out of 46 (32.6 per cent) cases with unilateral changes; while they disappeared in 19 out of 148 (12.8 per cent) cases with cavity images, in 11 out of 123 (8.9 per cent) cases with changes in total fields, and in 25 out of 147 (17.0 per cent) cases with bilateral changes. Although no parallel relation was recognized between the number of tubercle bacilli before treatment and their disappearance, yet their disappearance in 18 out of 112 (16.1 per cent) cases, which had corresponded to Gaffky VII-X, was notable. Cavity images disappeared in 18 out of 148 (12.2 per cent) cases, and infiltration shadows without cavity images were remarkably absorbed or disappeared in 27 out of 45 (60.0 per cent) cases. It is suggested that the side chains of the fatty acids might play an important rôle in the diminution of tubercle bacilli.—*Über die chemotherapeutische Anwendung von l-Rhodinsäure, einem Bestandteil des Oels vom Taiwankhinoki-Baum, und von einigen anderen Fettsäuren naheverwandter abnormer Struktur bei tuberkulösen Patienten*. (Zweite Mitteilung), S. Katsura, T. Nozoe & co-workers, *Studia Medicinæ Tropicalis, Supplementum I*, 1944, 1: 352.—(E. R. Long)

**Streptomycin and Promizole in Tuberculous Meningitis.**—Seven children with tuberculous meningitis were treated with streptomycin and promizole. Promizole was administered

orally at six or twelve hour intervals. The total daily dosage was 0.5 to 1.0 g. The daily dose was gradually increased until a blood level of 2 to 3 mg. per hundred cubic centimeters was obtained. The dosage of streptomycin was 0.5 to 1.0 g. in infants and small children, and 2 g. in older children. It was administered in divided doses at six hour intervals. In most cases 0.1 g. of streptomycin intrathecally on alternate days was well tolerated for about six weeks. Intrathecal therapy was then given only every third or fourth day amounting to a total of twenty-five to forty injections. No serious toxic effects of promizole were noted. One patient died while 6 are living three to eight months after treatment was instituted. The only neurologic sequelae are strabismus in one case and transient coarse tremors in another. The sugar content of the spinal fluid returned to normal in three to twelve weeks.—*Tuberculous Meningitis in Children, A Preliminary Report of its Treatment with Streptomycin and 'Promizole', Edith M. Lincon, T. W. Krimse & Estelle De Vito, J. A. M. A., February 28, 1948, 136: 593.*—(H. Abeles)

**Streptomycin in Tuberculous Meningitis.**—This article deals with the use of streptomycin in tuberculous meningitis as seen in children. Symptoms which should immediately make one suspect meningitis in tuberculin-positive children are headache, vomiting, sudden anorexia, fever (which is always present), and emaciation. Symptoms of longer standing, in addition to the above, will include personality changes and insomnia. Lumbar puncture should be a routine procedure which may have to be repeated. Choroidal tubercles and changes in the optic disk are frequently discovered. Forty-one of 90 cases acid-fast bacilli were found in the spinal fluid, and in 4 of 90 cases the Pirquet test was negative but the intradermal reaction was positive. Therefore, it is concluded that streptomycin should not be withheld if acid-fast bacilli are not recovered. Under streptomycin treatment, cases may terminate as follows: (1) deterioration whatever action is

taken; (2) encouraging improvement but ultimate chronicity; (3) favorable progress and return to excellent health. In the last instance it cannot be known whether relapses will occur. At the beginning of this series, large doses of 100,000 to 200,000 units per kilogram per day were administered, along with intraspinal injections. With such large doses it becomes impossible to distinguish between symptoms and signs caused by the drug or by the disease. Large doses injected intraspinally always produce violent histological reactions, with lymphocyte counts ranging from 50 to 800 cells per cm. The dose of streptomycin in the latter half of the series was reduced to 100,000 units per kilogram per day parenterally and 50,000 to 100,000 units per day intraspinally during the first several days or week. This was again reduced to 50,000 units per kilo per day parenterally with no spinal injections. Under treatment, choroidal tubercles lose their original aspect and gradually heal or disappear, leaving residual pigment. The cell count in the spinal fluid returns to normal or subnormal, always below 10 and generally under 4. This occurred in 16 of the cases under observation. At the present time 46 children who have been undergoing treatment for from two to ten months appear to be normal. Treatment is stopped when there is an absence of all clinical meningeal symptoms, an ascending weight curve, complete apyrexia, normal sedimentation rate, a spinal lymphocyte count below 10 per cm., absence of tubercle bacilli in culture, and, if possible, a normal quantity of cerebrospinal albumin. A group of patients apparently cured of tuberculous meningitis, but still having symptoms and positive neurological signs, constitute a serious problem. It was decided to operate in 6 of these cases. In 5 of these, widespread leptomeningitis or pachymeningitis of the cisterna pontis was found; in the 6th there was a large meningeal tubercle about the chiasma. In 2 of these cases the results were remarkable. One patient, who was comatose and blind at the time of operation, is one who now gives the greatest hope of recovery.—*Streptomycin and Tuberculous*

*Meningitis in Children, Preliminary Note, R. D. St. Thieffry, E. Brissaud & H. Noufflard, Brit. M. J., December 6, 1947, 4535: 897.*—(R. W. Clarke)

**Pressure Breathing and Circulation.**—Simultaneous measurements were made during pressure breathing of the increase in volume of the lower leg, which was enclosed in a plethysmograph, and of the increase in weight of the caudal end of the body as indicated by the change in balance of a teeter-board on which the subject lay supine. From these results it may be calculated that an increase of pulmonary pressure of 30 cm. of water displaces 500 cc., or about half of the blood contained in the lungs; this represents about 8 to 10 per cent of the total blood volume. About 3 per cent of the total blood volume goes into the extremities and the remainder into the abdomen. In the standing position, there is less blood in the lungs, and the amount which can be displaced by pressure breathing is correspondingly less. By the use of a boot plethysmograph it is shown that the onset of pressure breathing causes an increase in foot volume due to passive inflation of the veins. If these passive changes are avoided by the previous inflation of a pneumatic cuff at 60 mm. Hg placed on the leg above the plethysmograph, then the onset of pressure breathing causes a decrease in the volume of the leg due to vasoconstriction. (Authors' Summary).—*Displacement of Blood from the Lungs by Pressure Breathing, W. O. Fenn, A. B. Otis, H. Rahn, L. E. Chadwick & A. H. Hegnauer, Am. J. Physiol., December, 1947, 151: 258.*—(G. C. Leiner)

**Pressure Breathing and Circulation.**—Positive pressure breathing produces vasoconstriction in the fingers and, therefore, a decrease in the finger pulse volume and a decrease in blood flow through the fingers.—*Effect of Pressure Breathing on Blood Flow through the Finger, W. O. Fenn & L. E. Chadwick, Am. J. Physiol., December, 1947, 151: 270.*—(G. C. Leiner)

**BCG Vaccination.**—During 1924 to 1926, all new student nurses were given a Pirquet test immediately before assuming their duties among tuberculous patients. Very few clinical cases developed in the positive group, but many did in the negative group. In 1927, of 57 nonreactors, 45 consented to be vaccinated with BCG. During subsequent years, the same policy of offering BCG to non-reactors was followed. Each year, the morbidity in the vaccinated group was much less than in the nonvaccinated group and often as low as in the Pirquet-positive group. The protective effect of BCG appeared to be durable.—*B.C.G. Vaccination of Nurses, J. Heimbeck, Tubercle, April, 1948, 29: 84.*—(A. G. Cohen)

**Apparatus for Airborne Infection.**—The author describes in detail an apparatus by means of which animals can be safely exposed to known numbers of droplet nuclei containing various infective agents. This is particularly suitable for quantitative natural airborne tuberculous infection. Only the fundamental principles of the device can be described here. A constant number of droplet nuclei of the infectious agent, engendered by atomizing a suspension of the agent with compressed air through a specially designed nozzle, is introduced into a chamber in which the animals are exposed, together with a constant flow of room air which is drawn into the chamber by draught action of a hot flame at the bottom of a specially constructed chimney which incinerates the outflowing infected air. The concentration of the infectious agent inhaled by the exposed animals is determined by the Wells air centrifuge. The tidal air of animals exposed can be measured during their sojourn in the apparatus. The entire system works under negative pressure and thus minimizes the hazard to the personnel. The instrument has been calibrated for the administration of minimal doses of tubercle bacilli to rabbits. It has been used for the study of the behaviour of inhaled particles in different states of suspension, as well as for the study of primary and reinfection tubercu

losis.—*On the Mechanics of Droplet Nuclei Infection. I. Apparatus for the Quantitative Study of Droplet Nuclei Infection in Animals*, W. F. Wells, *Am. J. Hyg.*, January, 1948, 47: 1.—(Max B. Lurie)

**Quantitative Relation between Inhaled Tubercle Bacilli and the Resulting Tubercles.**—Particles containing bovine tubercle bacilli of such a size that they settled less than one-tenth of a foot per minute in still air were introduced into the apparatus described in the preceding paper. If such particles containing single bacilli are inhaled by rabbits, it is claimed that each organism will give rise to a tubercle in the lung. If the particles are coarse so that they settle one foot per minute, only one in ten such particles will induce a tubercle in the lungs of rabbits; the remainder are swallowed. As has been proven many times before, it is shown here again that a first infection protects from a subsequent inhalation reinfection. The theoretical basis for the above conclusions must be pursued in the paper proper. *On the Mechanics of Droplet Nuclei Infection. II. Quantitative Experimental Air-Borne Tuberculosis in Rabbits*, W. F. Wells, H. L. Ratcliffe & C. Crumb, *Am. J. Hyg.*, January, 1948, 47: 11.—(Max B. Lurie)

**Tomography of the Spine in Tuberculous Disease.**—Tuberculosis of the spine is first noticeable in the X-ray as the diminution of the space between the vertebral bodies with decalcification of the adjacent portions of bone. As caries progresses some collapse occurs and several vertebral bodies may be involved. Ordinary anteroposterior and lateral X-rays are useful in finding the extent and progress of the disease. Tomography is of special value, however, in overcoming difficulty in such areas as the first and second cervical vertebrae, the cervical dorsal region, and the lumbosacral area, where overlapping structures may interfere in delineation of bony disease. In the region of the first and second cervical vertebrae, a good view of the diseased area may be obtained from an ordinary lateral film,

but in the anteroposterior X-ray, the area is usually obscured by the lower jaw. In the cervical dorsal region, tuberculous disease may be delineated with plain films, but tomography may be very helpful in more accurate definition. Tuberculous disease of the sacrum is rare except in conjunction with disease of the sacroiliac joints. Tomograms may be of value in special cases. A brief description of the radiographic technique is given.—*Tomography of the Spine in Tuberculous Disease*, S. G. Wood & M. C. Wilkinson, *Brit. J. Radiol.*, October, 1947, 20: 418.—(L. Hyde)

**Lung Abscess.**—During a period of ten years, pulmonary resection for lung abscess was performed in 37 cases. This number includes only those which appeared to be abscess cases from the very beginning, and not secondary to other conditions. The patients had all received medical treatment, often including bronchoscopic aspiration and the use of sulfonamide drugs and penicillin. The condition developed in the course of respiratory infection in 20 cases, following inhalation anesthesia in 11, complicating a foreign body in 5, and after a chest injury in one. Seven patients had had previous surgical therapy consisting of artificial pneumothorax in 2, rib resection and drainage in 3, drainage of empyema in one and drainage and thoracoplasty in one. The average time from diagnosis to resection was eighteen months. The operation consisted of segmental resection in 2, lobectomy in 16 and bilobectomy in 3 cases. Of these 21 cases, there was one operative death. Complications occurred in 3 cases, all of which responded to treatment. Pneumonectomy was performed in 16 cases. There were 6 operative deaths. In addition, 3 patients died of brain abscess within five months. Additional, nonfatal complications were noted in 3 cases. The recent trend in the treatment of chronic lung abscess is away from drainage and toward resection. The stated indications for resection are: (1) persistent symptoms due to pathological changes secondary to open drainage; (2) multiple or multilobular

abscesses; (3) abscesses associated with secondary changes, consisting of fibrosis, bronchiectasis, bronchostenosis and atelectasis; (4) abscesses so located anatomically as to be inaccessible to adequate drainage; (5) abscesses in which the diagnosis of malignancy is entertained; (6) abscesses associated from the onset with excessive bleeding; (7) abscesses in children; (8) abscesses secondary to foreign bodies not removable by bronchoscopy. —*Pulmonary Resection for Abscess of The Lung*, R. P. Glover & O. T. Clagett, *Surg., Gynec. & Obst.*, April, 1948, 86: 385.—(A. G. Cohen)

**Cough as a Symptom.**—Cough is dependent upon a local stimulus which originates nerve reflexes through the medulla. The act of coughing can be divided into three phases: (1) the inspiratory phase, followed by (2) the compressive phase which depends upon the closure of the glottis and an increase in the intrapulmonary pressure immediately preceding expiration, and (3) the expiratory phase, when the vocal cords and ventricular bands are quickly separated and air is forced out with the production of characteristic cough sounds. Purpose of cough is the removal of mucus, inflammatory exudate, and any other material in the air passages. The rôle played by bronchial movements during respiration is extremely important in the removal of secretions from the air passages. Deep inspiration increases the motion of the bronchial walls and this tends to move bronchial secretions. The degree of mobility is practically negligible during quiet respiration, such as is observed in narcosis, acute pleurisy and injuries to the chest. Ciliary function is also important in the elimination of secretions from the air passages. It is more effective in the presence of thin than of thick secretions. Cough is a symptom and the cause must be determined. It may be caused by common respiratory tract disease, smoking, exposure to dust and fumes, extra-respiratory factors ("ear cough" or "reflex aural cough"), diseases of the nose and nasal accessory sinuses, nasal or pharyngeal obstruction,

aspiration of food or fluid, and allergy. Cough of functional origin occurs, but one must be careful to exclude all possible organic causes before arriving at this diagnosis. To determine the exact cause of cough, careful history and physical examination are necessary. Examination of the ear, nose and throat, and chest, plus chest X-rays, are usually indicated. Bronchography is indicated if there is any suspicion of increased bronchopulmonary markings suggesting bronchiectasis. In the presence of a history of allergy, appropriate tests must be performed. Treatment must be directed at the cause. Cough is necessary to rid the tracheal bronchial tree of excessive secretions, for example, from pulmonary abscess or bronchiectasis, and in these conditions narcotics should be used sparingly if at all. On the other hand in carcinoma cough is quite purposeless, and therefore symptomatic therapy and suppression may be indicated. When cough is inadequate due to thick tenacious secretions, so-called stimulating expectorants are recommended. Inhalations of carbon dioxide and oxygen increase the quantity of sputum and have been highly recommended.—*Cough as a Symptom*, L. H. Clerf, *M. Clin. North America*, November, 1947, 31: 1993.—(L. Hyde)

**Cryptococcosis.**—The case history of a girl whose disease started in 1937, and who was first reported in 1941, is reviewed. In 1938, *Cryptococcus hominis* was found in the material drained from a chest sinus and in the spinal fluid. Since then the patient has had several courses of sulfadiazine treatment; the lesions in the chest have improved while the changes in the central nervous system have shown slow progression. The patient is alive nine years after the onset of symptoms. On the basis of experiments on rats infected with cultures of *Cryptococcus hominis*, the following conclusions are made: "Animals previously infected with the cryptococcus and clinically appearing well gave no sign of having developed antibody protection against that organism. Animals treated with sulfadiazine



had their life expectancy increased from 11.4 to 28.9 days. Animals treated with penicillin had their life expectancy increased from 11.4 to 22.6 days. No advantage accrued when penicillin and sulfadiazine were used in combination. Animals treated with streptomycin had their life expectancy increased from 11.4 to 28.0 days."—*Cryptococcosis. Report of a Case and Experimental Studies, E. B. Reilly & E. L. Artman, Arch. Int. Med., January, 1948, 81: 1.*—(G. C. Leiner)

**Pericarditis following Upper Respiratory Infection.**—A 52-year-old man developed tonsillitis with fever. Within three weeks pericarditis with effusion had occurred. Culture of the fluid showed hemolytic streptococcus. Repeated cultures from an accompanying pleural effusion were sterile. The patient recovered completely after two courses of penicillin treatment.—*Pericardial Effusion due to Hemolytic Streptococcus following an Acute Upper Respiratory Infection; Associated Pleural Effusion; Report of Case and Review of Literature, S. H. Rinzler & S. Leibowitz, Am. Heart J., March, 1948, 35: 490.*—(G. C. Leiner)

**Mediastinitis.**—Two cases of mediastinitis in children are reported. Both followed the ingestion of baby food from containers from which glass had been chipped when the containers were opened. One case was proved to be due to the ingestion of the glass fragment, while the other was presumably due to the same type of fragment (Author's Summary).—*Mediastinitis due to Ingestion of Glass, J. D. Steele, J. A. M. A., February 21, 1948, 136: 554.*—(H. Abeles)

**Mediastinotomy.**—A case of spontaneous mediastinal emphysema requiring mediastinotomy is presented. The clinical picture, diagnosis and management are discussed (Authors' Summary).—*Mediastinotomy in Spontaneous Mediastinal Emphysema, J. R. Karns & E. O. Daue, Jr., J. A. M. A., February 28, 1948, 136: 622.*—(H. Abeles)

**Silicosis.**—Every new person employed in the Calumet industrial area was given a physical and X-ray examination. The films were graded on the basis of the extent of lung markings plus the size of lymph nodes. There was a fairly close correlation between the extent of these changes and the length of time a person had worked in this area. These changes were not disqualifying. Apical scarring or other evidence of tuberculosis was disqualifying. Repeat X-rays were taken every year. The earliest changes resulting from dust were seen in six years, with an average of fifteen years. The changes consisted of enlargement and thickening of the hilar nodes. These were termed potential primary silicosis, and were not associated with symptoms. If the changes were progressive in workers under 45 years of age, removal from exposure to silica was advised. If over 45, the workers were allowed to continue unless there was evidence of pulmonary infection. A definite diagnosis of silicosis was not made unless there was nodule formation in the parenchyma. The onset of tuberculosis was very insidious. Aluminum therapy was provided on a voluntary basis; treatment was not given if there was evidence of tuberculosis. In the prophylactic group 30 to 40 treatments were given annually while in the therapeutic group, 40 treatments were given. Treatment consisted of the inhalation of aluminum dust or oxide through the mouth. The first treatment lasted two to three minutes. The time was gradually increased to ten minutes by the eighth treatment and so continued. There were no toxic reactions. It is believed that the progression of the silicosis was checked markedly by aluminum therapy and that the incidence of secondary tuberculosis was much less. The authors are not certain of the benefits of prophylaxis, but believe them to be good.—*Silicosis Study and Management in the Calumet Industrial Area, C. W. Rauschenbach, D. R. Johns, J. F. Larabee, L. M. Hammar & B. F. Poracky, Indust. Med., January, 1948, 17: 1.*—(A. G. Cohen)

# THE PATHOGENESIS OF MINIMAL PULMONARY TUBERCULOSIS<sup>1,2</sup>

A Study of 1,225 Necropsies in Cases of Sudden and Unexpected Death

E. M. MEDLAR<sup>3, 4, 5</sup>

## INTRODUCTION

The understanding of any illness is enhanced by an appreciation of its pathogenesis and further clarification is obtained by an appropriate terminology that indicates the different phases of that pathogenesis. The terms that are chosen should be as concise and as few in number as is consistent with a clear portrayal of the pathogenesis. In tuberculosis the terminology is redundant, the terms too often are applied incorrectly, and as a result confusion exists in the understanding of the disease. As this paper deals with the pathogenesis of *minimal* tuberculosis, it seems appropriate at this time that a pathologist should define the terms employed commonly by clinicians, roentgenologists and epidemiologists in discussions on tuberculosis, for the majority of the terms have been taken from the terminology created by pathologists. It is recommended that some of the terms defined be discarded; nevertheless it is necessary to define and discuss them to justify their deletion.

### *Definition of Terms*

The terms *exudative*, *caseous*, *ulcerative*, *fibro-caseous*, *fibro-caseo-calcific*, *fibro-calcific*, and *fibrotic* are used by the pathologist to indicate different phases in the pathogenesis of a tuberculous lesion with an appreciation that no one phase is completely independent of its predecessor and that all tuberculous lesions do not necessarily undergo the same evolution. These terms are defined in the sequence in which they usually occur in the pathogenesis of a lesion and they apply equally to a lesion whether it be 1 mm. or 2 cm. in diameter.

A tuberculous lesion may be described in the following terms.

*Exudative:* The term exudative is used to designate the accumulation of the elements of inflammation at the site of infection. The intense vascular congestion and the abundant exudation of fluid that is common in the early phase of inflammation in many bacterial infections, *e.g.*, pneumococcus, are absent in infections with the tubercle bacillus except where abrupt massive endobronchial metastases occur. This accounts for the "dryness" of most tuberculous lesions. Nevertheless the emigration of leucocytes from the circulating blood begins early and continues to a greater or lesser degree until complete healing of a lesion by

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resolution or by fibrosis has occurred. The types of leucocytes and the numbers of each type in the exudate vary from time to time. Initially, the polymorphonuclear leucocyte is the chief component and, if the lesion develops rapidly, it continues to predominate. Frequently this leads to the formation of a tuberculous abscess that differs in certain respects from other bacterial abscesses, *e.g.*, those caused by *Staphylococcus* or *E. coli*. The chief characteristic of a tuberculous abscess is the slowness with which it liquefies. Although liquefaction may occur fairly promptly, usually it is considerably retarded and it even may not occur at all. In the latter instance, the formation of the abscess is checked or aborted although all the essentials for an abscess are present except the completed process of liquefaction.

If the progress of the lesion is less rapid, the epithelioid cell (a modified monocyte of the circulating blood) may outnumber the polymorphonuclear leucocyte for a time, only to be surpassed by the latter cell type if the tubercle bacilli begin to multiply rapidly. In a later stage, when repair of the lesion becomes manifest, monocytes and then lymphocytes predominate, with the lymphocyte the last of the cells of inflammation to vanish with a complete healing of the lesion.

When a pathologist uses the term exudative he implies that the lesion has not necrosed. He is aware of the fact that all exudative lesions do not undergo necrosis and that the proportion of each leucocytic type in the exudate will shift as a lesion gradually resolves or is fibrosed.

*Caseous*: The term caseous refers to the necrosis of the content of a tuberculous abscess with or without liquefaction. In the lung this represents an area of necrotic tuberculous pneumonia. Lesions of this type may persist for a long time without liquefaction or they may liquefy and slough early. A tuberculoma is a discrete caseous lesion of some size.

*Ulcerative*: The term ulcerative is used to describe a liquefying caseous lesion that is being sloughed. This applies to an ulcer, as in a bronchus or intestine; or to a cavity, as in the lung or kidney parenchyma.

*Fibro-caseous*: An unsloughed caseous lesion that is being organized by fibrosis is designated fibro-caseous. The fibrosis begins in the periphery of the necrotic area and forms the so-called "capsule."

*Fibro-casco-calcific*: This term is used to describe a fibro-caseous lesion with calcium and other salt deposition in the caseous debris.

*Fibro-calcific*: A lesion in which the caseous debris has been completely replaced by calcium and other salts and fibrotic tissue is designated fibro-calcific.

*Fibrotic*: The term fibrotic refers to a lesion that is completely organized by fibrosis even if caseous material had been present.

It is not uncommon to find more than one and sometimes all of the phases defined above when a tuberculous lesion in the lung is observed at necropsy. When foci of fibrosis, caseation, fibro-caseation and fibro-calcification are all present, the lesion as a whole usually is described as *fibro-casco-calcific*. The terms *fibro-ulcerative phthisis* and *fibroid phthisis* are used frequently in a similar sense. The use of such a terminology provides the pathologist with a crude method of estimating the relative age of tuberculous lesions as a whole when groups of persons

of similar age are analyzed, but this does not imply that the pathologist can determine that all caseous or all fibro-calcific foci are of identical age.

*Productive tuberculosis:* The term productive tuberculosis is used by some pathologists. The concept conveyed by this term is that the tuberculous lesion results entirely from a proliferation of the tissue cells normally present in the area, hence the lesion is not inflammatory in character and cannot be considered exudative. This interpretation is responsible for the ideas that a fibrotic capsule is formed early in a tuberculous lesion; that the classic histologic tubercle, aside from its lymphocytic components, is a local hyperplasia of the tissue; that such a lesion is "closed"; that the destruction of the fibrotic capsule by "exudation" has to occur before the lesion can become "open"; and that the acute inflammatory reaction (exudation) is a response either to "tuberculin" escaping from the lesion (perifocal inflammation) or to an "acute" infection occurring in the area that contains the tuberculous lesion. This concept does not fit the known facts as of today relative to the pathogenesis of a tuberculous lesion and the term *productive tuberculosis* should be discarded.

*Classic histologic tubercle:* This term represents a phase in the pathogenesis of the disease that occurs commonly in the repair of a lesion. It is not of great significance except to the pathologist as a histologic confirmation of the diagnosis of tuberculosis. It can no longer be considered pathognomonic for tuberculosis as such lesions may be found in fungus infections.

The above terms, as used by clinicians and roentgenologists in the interpretation of roentgenographic shadows, should be used with care. The term *exudative tuberculosis* is used correctly when shadows of recent origin are interpreted, but it is not generally appreciated that stationary or even receding shadows may represent lesions that still are in large part exudative in character. *Caseation* cannot be differentiated from *exudation* by the character of roentgenographic shadows and it is doubtful that *fibrosis* can be distinguished from either *exudation* or *caseation* by this means. So-called calcific densities may prove to be more caseous than calcific. These remarks do not mean to imply that an individual experienced in reading roentgenograms cannot evaluate the clinical significance of certain shadow patterns, especially if serial roentgenograms are available, but they do imply that the composition of a tuberculous lesion cannot be determined with exactness from roentgenographic shadows. Terms other than pathologic ones should be used in describing roentgenographic shadows. It is suggested that the term *productive tuberculosis* be replaced by the term *fibrotic organization*, for this is the sense in which clinicians and roentgenologists commonly use the term rather than in the sense that pathologists employ it.

*Primary tuberculosis:* The term primary tuberculosis designates a first infection with the tubercle bacillus. In primary tuberculosis it is usual that lymph nodes become macroscopically enlarged and caseous as a reaction to lymph-borne infection from the site of the parenchymal focus. The combination of the parenchymal focus and the affected lymph node is known as a *primary complex*.

*Reinfection tuberculosis:* A new exogenous or air-borne infection in an in-

dividual that has completely healed a primary infection is known as reinfection tuberculosis. In reinfection tuberculosis it is unusual for the lymph nodes draining a parenchymal focus to show macroscopic evidence of tuberculous infection. To substantiate a diagnosis of reinfection tuberculosis, a healed primary infection must be demonstrated. Hence reinfection tuberculosis can be determined with certainty *only* at necropsy.

*Endogenous reinfection:* This term is used at times to describe evidence of new disease in an individual who has taken a "cure" or who has been clinically well despite the presence of roentgenographic shadows. The new disease may be of endogenous origin, but it is not a reinfection. The term *exacerbation of disease* is more appropriate in this connection.

*Superinfection:* A new exogenous infection in a person who already harbors an unhealed lesion would constitute a superinfection. There are clinicians and pathologists who believe that such a condition exists, but clinical or pathologic proof is most difficult, if not impossible, to obtain. If this term is used, care should be taken to indicate that the condition is an unproven hypothesis.

*Reinfection complex:* The term reinfection complex is used to describe a condition in which the lymph nodes draining a reinfection parenchymal lesion are affected macroscopically with tuberculosis that is in character with the parenchymal lesion. This condition, once thought to be rare, probably is more common than is realized at present. Its existence makes necessary a most critical study of tissues at necropsy to determine whether a primary or a reinfection disease is present. On occasion the lymph nodes may be enlarged sufficiently to cause a shadow to be cast on a roentgenogram and hence such shadows no longer can confirm unequivocally a diagnosis of primary tuberculosis in an adult.

*Incomplete primary complex:* This term designates a condition in which either the parenchymal or lymph node focus cannot be demonstrated at necropsy. This situation occurs sufficiently often to interfere with an accurate determination of the incidence of reinfection tuberculosis.

The terms *productive tuberculosis*, *endogenous reinfection*, *primary tuberculosis*, *reinfection type*, and *superinfection* often are used by clinicians and roentgenologists, and confusion exists because of the way in which they are applied. These terms should be used precisely or not at all. Excepting children, a clinical diagnosis of primary tuberculosis is permissible *only* if the disease is of recent origin in a person, usually a young adult, who was known to be a nonreactor to tuberculin at a previous date. Reinfection tuberculosis can be diagnosed *with certainty only at necropsy*. It may be surmised clinically when roentgenograms of the chest reveal shadows consistent with active tuberculosis in addition to shadows of calcific density disassociated from the active disease. Many individuals with reinfection tuberculosis, however, will fail to reveal foci of calcific density in roentgenograms. The term *endogenous reinfection* should be discarded altogether, and the term *superinfection* can serve no useful purpose for it represents an hypothesis that is impossible of proof on clinical grounds and is not proven on pathologic grounds. It is proposed that the term *fibrotic organization* replace *productive tuberculosis*.

*Lympho-hematogenous tuberculosis:* A condition in which tubercle bacilli are disseminated from a necrotic lymph node into large lymphatics and thence through the blood stream, constitutes lympho-hematogenous tuberculosis. There is pathologic evidence that this condition occurs but it can be determined *only at necropsy*. The common usage of this term in discussion of tuberculosis creates an impression that this condition occurs commonly in adults, whereas necropsy studies show that it is an unusual occurrence.

*Hematogenous tuberculosis:* Hematogenous tuberculosis is the result of the dissemination of tubercle bacilli through the blood stream, with tuberculous involvement of capillaries or small veins the usual source, and arteries an infrequent source, for the dissemination. Generalized miliary tuberculosis is one manifestation, and tuberculosis of the kidney and other organs without manifest generalized miliary disease, another manifestation of this condition. In generalized miliary tuberculosis the small lesions are seeded evenly throughout both lungs. Some clinicians and roentgenologists use the term *miliary* when the pulmonary lesions are small and numerous but are not distributed uniformly. In this instance it would be better to use the term *miliary endobronchial metastases* in order that an hematogenous origin is not inferred.

*Focal hematogenous pulmonary tuberculosis:* This term is used to describe localized tuberculosis in the upper lung fields and is commonly used by clinicians and roentgenologists in the interpretation of roentgenographic shadows in the upper lung field in cases that show no tuberculous cavity to suggest the probability of endobronchial metastasis. It is postulated commonly that such shadows represent a characteristic feature of lympho-hematogenous tuberculosis. Necropsy studies show that lympho-hematogenous tuberculosis is unusual in an adult and, when it does occur, a generalized miliary tuberculosis ensues with rare exception. There is no pathologic proof that, in lympho-hematogenous tuberculosis, the bacilli are screened out in a focal manner in the lungs. The only other source for a focal hematogenous pulmonary tuberculosis would be a tuberculous ulceration of a pulmonary artery. This occurs rarely and in such instances a generalized miliary tuberculosis ensues. There is evidence from necropsy studies, however, that: focal pulmonary lesions occur commonly in the upper part of lungs without tuberculous lesions in other organs; that these lesions frequently contain caseous and ulcerative foci; and that endobronchial metastases commonly arise from such lesions. To surmise that these focal lesions are of hematogenous origin carries with it the serious implication that a general hematogenous dissemination of bacilli has occurred; whereas, in the majority of instances, necropsy studies show that such lesions are limited to the lung. The term *focal hematogenous pulmonary tuberculosis* represents a postulate that has little, if any, pathologic fact to substantiate it.

*Metastatic tuberculosis:* The term metastatic tuberculosis designates any tuberculous lesion derived from the initial focus without regard to the method of transmission. Tuberculous lesions observed clinically are, with rare exceptions, metastatic lesions and they are common in both primary and reinfection tuberculosis. The mode of transmission may be indicated by the qualifying

adjectives endobronchial, lymphatic or hematogenous. These terms may replace such terms as "spread," postprimary complication, primary renal tuberculosis, et cetera, that now are used. An objection to the term postprimary is that it implies a healed primary focus, a condition that often is not the case. Tuberculosis of the conjunctiva and of the skin may be implanted from without. Tuberculosis of the bronchi, trachea, larynx, ureter, and genital organs may be regarded as metastatic lesions as they result commonly from the draining of a focus through natural ducts. Primary tuberculosis of the intestine is implanted from without, but the lesions commonly found in tuberculous individuals should be regarded as metastatic foci as they usually are dependent upon a sloughing pulmonary lesion.

*Tuberculous infection and tuberculous disease:* By common usage, the term *tuberculous infection* refers to cases that reveal roentgenographic shadows with certain characteristics in the upper lung fields, and from experience it has been found that cases with roentgenographic shadows of such characteristics generally are not in need of close clinical supervision. Such cases are interpreted often as "healed" or "obsolete" tuberculosis, whereas necropsy studies show that completely healed tuberculosis is found infrequently in this part of the lung and that usually caseous, and often ulcerative, lesions are present. The term *tuberculous disease* is used commonly when roentgenographic shadows with certain characteristics that have been found from experience to indicate the presence of dangerous disease are present, and in this sense necropsy studies afford data that concur.

In a pathogenetic sense, *tuberculous infection* and *tuberculous disease* are synonymous with the outcome of the infection determined by the natural or acquired resistance of the individual. The common usage of these terms artificially separates infection and disease and, because of the nature of the pathology in tuberculous cases, such an artificial separation can hinder materially an effective control of the disease unless the actual condition is appreciated generally. Cases now classified as *tuberculous infection* will be, of course, clinically well and will not need hospital care. It is impossible, however, to determine beforehand which one or how many may suffer a relapse of the disease and, because of this situation, some sort of supervision by roentgenographic study should be devised.

The terms that have been defined and discussed represent, in large part, those now in common use in the United States. The changes that are suggested refer to a clarification of a confused condition. Many terms that are used by pathologists and clinicians have not been included, for the terminology in tuberculosis is redundant and is in need of simplification. The descriptive terms used in the following paper are in compliance with the definitions offered.

#### PATHOGENETIC ANALYSIS OF MINIMAL TUBERCULOSIS

The importance of detecting pulmonary tuberculosis early has implemented mass roentgenographic surveys which have disclosed lesions of minimal extent in surprisingly large numbers. Reisner and Downes (1) found that 65 per cent of the individuals who exhibited roentgenographic shadows after exposure to

known cases of tuberculosis had lesions of minimal extent and Edwards (2), in a general survey, observed that 70 per cent of the newly discovered cases were of minimal extent. Elkin, et al. (3), in a roentgenological survey of persons employed in factories producing war equipment found that 70 per cent of the new cases were minimal in extent and that in white males the incidence of radiographic shadows increased from 0.3 per cent in those less than 20 years of age to 9.4 per cent in those over 60 years of age.

The disposition of the newly discovered minimal case presents a problem more subtle than the problem of detection because the implications of lesions of this extent are difficult to determine. This is due, in part at least, to a widespread and distressing lack of understanding of the pathogenesis of the disease. Roentgenographic shadows of this extent are interpreted, depending on the character of the shadow and the concept of the interpreter, as exudative, productive, fibro-caseous, calcified, fibrotic, healed, obsolete, of no clinical significance, soft, hard, stringy, clinically active or clinically inactive. As a rule only those individuals with soft, exudative, or clinically active lesions are considered in need of medical supervision and often lesions of this character are not taken seriously.

A survey of the literature fails to reveal a pathogenetic analysis of a series of cases that could be considered as representative of the lesions of minimal tuberculosis found in mass roentgenographic surveys. The most meticulous anatomical studies of tuberculous lesions, observed in persons dead from causes other than tuberculosis, reported in the United States, are those of Terplan (4), Sweany (5), Carnes (6), and Everett (7). None of these authors has reported on more than individual cases that would conform to a clinical interpretation of pulmonary tuberculosis of minimal extent.

#### MATERIAL AND METHOD

Through the courtesy of the Office of the Medical Examiner of the Borough of Manhattan, the writer has had the opportunity to collect data relative to the incidence of tuberculous infection from 1,225 necropsies on adults over 20 years of age who died suddenly and unexpectedly. Among these persons there were a number in whom the extent of the tuberculous disease would conform to the standard for minimal pulmonary tuberculosis detailed in the Diagnostic Standards of the National Tuberculosis Association (8). An analysis of these minimal cases is the object of this paper.

The value of any study of necropsy material dealing with tuberculosis depends upon the care and the time spent in the search for evidence, not alone in the lungs but also in the abdominal viscera and in the various lymph nodes associated with the respiratory and gastro-intestinal systems. In collecting the data on which this paper is based, the writer has been free to devote his entire time to a search for evidence of tuberculosis without having to assume responsibility for the performance of the necropsy or of recording the necropsy findings. At least two hours were spent in the examination of the fresh tissues in every case. It required two and one-half years to collect the data on which this study is based.



At the time of the necropsy the lymph nodes were cut into thin layers with a scalpel and the lungs and abdominal organs were cut into sections approximately 3 mm. thick. All sections of tissue were palpated with bare fingers in search of minute tuberculous lesions, and tuberculous foci 1 mm. or less in diameter were often discovered by this method. Not infrequently the only evidence of tuberculosis in lymph nodes was a small sliver of calcified material in a single node of normal size. The utilization of this technique in the routine examination of fresh tissues was preferred as it avoids the delay inherent in obtaining roentgenographic films, and about the only advantage of a roentgenogram is the prompt location of calcific foci. It is doubted that a significant number of calcific lesions have been missed in the method employed and many noncalcific lesions less than 2 mm. in diameter were discovered. It is believed that the minute noncalcific lesions would fail to register a significant shadow on a roentgenogram.

The observations in each case were recorded on a separate sheet of paper on which there was an outline of the lungs. The relative size, macroscopic character and location of every lesion, the date, name, age, sex, race and cause of death were recorded. The larger foci were examined for evidence of cavity formation, caseous foci and calcific deposits and many blocks of tissue from each case were preserved for microscopic study.

### *Criteria for Selection of Cases*

It is believed that some sort of a roentgenographic shadow would have been seen in each case included in this study had roentgenograms of the chest been available. The selection of cases rests upon the investigator's own judgment and not on established fact from a roentgenological standpoint. In the necropsy series there were many cases with tuberculous foci that were considered too small to register a significant roentgenographic shadow and these were all rejected from the study. In the group of minimal pulmonary tuberculosis selected for study the smallest lesion included involved at least a cubic centimeter of lung parenchyma with one or more foci, and the largest lesion was within the limits of minimal disease as defined in the Diagnostic Standards of the National Tuberculosis Association (8). To preclude the question as to whether the lesions were tuberculous, all lesions included in the study contained caseous foci, calcific foci or both. Focal scars without evidence of caseation or of calcification were rejected as they could not be proved to be of tuberculous origin. This was done despite the fact that many such foci were regarded as healed areas of tuberculosis. Lesions with cavities less than 1 cm. in diameter were included, even though a minimal lesion by definition should not contain a cavity. The presence of the cavities that were included would be most difficult, if not impossible, to demonstrate in a roentgenogram of the chest because of their small size and of their location in the lung.

The separation of the cases of minimal pulmonary tuberculosis into *primary* and *reinfection* groups and the behavior of these groups is an important part of the study. The criterion for the inclusion of any case in the *primary* group is that the lymph nodes draining the area of parenchymal disease must show evidence of tuberculous involvement with no calcific or other foci in lungs, lymph nodes, or gastro-intestinal tract disassociated from the lesion under study. In the *reinfection* group at least one calcified *primary complex*, disassociated from

the lesion under study, must be present and, if the lymph nodes draining the area of the parenchymal focus are tuberculous, they must present a condition consistent with the predominant feature of the lesion under study.

To afford a comparison of minimal pulmonary tuberculosis with calcified primary parenchymal foci, cases were selected on the basis that one calcified primary complex, and no other evidence of tuberculous infection in the lungs or lymph nodes, was present. On the assumption that calcific foci over 2 mm. in diameter would be observed usually in roentgenograms of the chest, no parenchymal lesion of smaller size was allowed and this restriction excluded a considerable number of cases with a single calcified primary complex. Any case that showed calcified lesions in lymph nodes of the neck was not acceptable for this group.

The terminology used in describing lesions and in other ways is in compliance with the terms previously defined in this paper. In all of the tuberculous lesions there were multiple tuberculous foci, hence the predominant features of a lesion as a whole are indicated by the term that is used in describing it. Thus, a fibro-caseous lesion is predominantly of this character and a fibro-caseo-calcific lesion evidenced foci of caseation, fibrosis and fibro-calcification.

#### OBSERVATIONS

Among the 1,225 necropsies there were 105 persons with a single calcified primary complex and 104 persons with a minimal disease that conformed to the criteria given above. In the minimal group, the disease was interpreted as representing either *primary* or *reinfection* disease in 96 persons and was indeterminate in 8 persons because no lymph node involvement was found. The indeterminate cases were deleted from the study. In addition, 28 persons had parenchymal scars at least 1 cm. in diameter with neither caseous nor calcific foci present and, as these scars could not be proved to be healed tuberculous foci, they are not included in this study. In the following pages an analysis of the 105 cases with a single calcified primary complex and of the 96 cases with minimal pulmonary tuberculosis is presented with regard to age, sex, race, and location and predominant features of the lesions.

The data presented in table 1 are in relation to race, sex and age with the percentages being of the necropsy series as a whole. The most important facts contained in this table are: calcified primary complexes are twice as frequent in persons over 40 as in those under 40 years of age with this situation being more pronounced in the Negro race and in all males; primary lesions of minimal extent are 2.7 times more frequent in persons less than 40 than in those over 40 years of age, being more pronounced in the Negro race and in all males; and reinfection lesions of minimal extent are found 10 times more often in persons over 40 than in persons less than 40 years of age with the white race and the white male contributing over 80 per cent of the cases in this category.

In the group of cases of minimal extent, the lesion was primary in type in 91 per cent of the persons less than 40 years of age, and reinfection in type in 72.6 per cent of the persons over 40 years of age. Both types of lesion were present

in all age groups, but it is evident that primary and reinfection tuberculosis predominate in different age groups. Tuberculous foci of macroscopic size were observed in the abdominal organs in 11 (26.8 per cent) persons in the pri-

TABLE 1

*Distribution of calcified primary foci, 2 mm. or more in diameter, primary and reinfection minimal pulmonary tuberculosis in relation to age, race and sex*

| AGE           | ALL<br>NECROPSIES | CALCIFIED PRIMARY<br>COMPLEX |          | PRIMARY MINIMAL<br>PULMONARY<br>TUBERCULOSIS |          | REINFECTION MINIMAL<br>PULMONARY<br>TUBERCULOSIS |          |
|---------------|-------------------|------------------------------|----------|--|----------|--|----------|
|               |                   | Number                       | Per cent | Number                                       | Per cent | Number   | Per cent |
| All cases     |                   |                              |          |  |          |  |          |
| All ages..... | 1,225             | 105                          | 8.5      | 41   | 3.3      | 55   | 4.5      |
| 20 to 39..... | 348               | 16                           | 4.6      | 21   | 6.0      | 2  | 0.6      |
| 40 to 59..... | 568               | 58                           | 10.2     | 13   | 2.3      | 29   | 5.1      |
| 60 +.....     | 309               | 31                           | 10.0     | 7  | 2.2      | 24   | 7.7      |
| White race    |                   |                              |          |  |          |  |          |
| All ages..... | 981               | 93                           | 9.4      | 28   | 2.8      | 51   | 5.2      |
| 20 to 39..... | 217               | 15                           | 6.9      | 11   | 5.1      | 1  | 0.4      |
| 40 to 59..... | 473               | 49                           | 10.3     | 10   | 2.1      | 27   | 5.7      |
| 60 +.....     | 291               | 29                           | 9.9      | 7  | 2.2      | 23   | 7.9      |
| Negro race    |                   |                              |          |  |          |  |          |
| All ages..... | 244               | 12                           | 4.9      | 13   | 5.3      | 4  | 1.6      |
| 20 to 39..... | 131               | 1                            | 0.7      | 10   | 7.6      | 1  | 0.7      |
| 40 to 59..... | 95                | 9                            | 9.4      | 3  | 3.1      | 2  | 2.1      |
| 60 +.....     | 18                | 2                            | 11.1     | —  | —        | 1  | 5.5      |
| Males         |                   |                              |          |  |          |  |          |
| All ages..... | 907               | 76                           | 8.4      | 29   | 3.2      | 49   | 5.6      |
| 20 to 39..... | 201               | 7                            | 3.4      | 15   | 7.4      | 2  | 1.0      |
| 40 to 59..... | 459               | 46                           | 10.0     | 9  | 1.9      | 27   | 5.9      |
| 60 +.....     | 247               | 23                           | 9.9      | 5  | 2.1      | 20   | 8.5      |
| Females       |                   |                              |          |  |          |  |          |
| All ages..... | 318               | 29                           | 9.1      | 12   | 3.8      | 6  | 1.9      |
| 20 to 39..... | 147               | 9                            | 6.1      | 6  | 4.1      | —  | —        |
| 40 to 59..... | 109               | 12                           | 11.0     | 4  | 3.6      | 2  | 1.8      |
| 60 +.....     | 62                | 8                            | 12.9     | 2  | 3.2      | 4  | 6.4      |

Percentages are those of all necropsies in specified groups.

mary group and in only one (3.6 per cent) person in the reinfection group. This suggests that adults with primary disease of minimal extent are less able to limit the infection to the respiratory tract than those with the reinfection type.

Nine (8.8 per cent) persons in the healed primary complex group had old

fibrotic or calcified tuberculous foci in one or more of the abdominal organs. In this group it appears that the blood-borne infection originated in the parenchymal pulmonary focus as this was the only focus in the lung. A similar origin for the hematogenous distribution in the primary group of minimal extent seems plausible.

The difference in age distribution of the primary and reinfection cases may be seen in figure 1. The increased incidence of calcific foci with increase in age reduces the number of persons in the older age groups in whom a primary infection would be possible and this may account for a lower incidence of primary lesions of minimal extent in older persons. If this explanation is correct, then

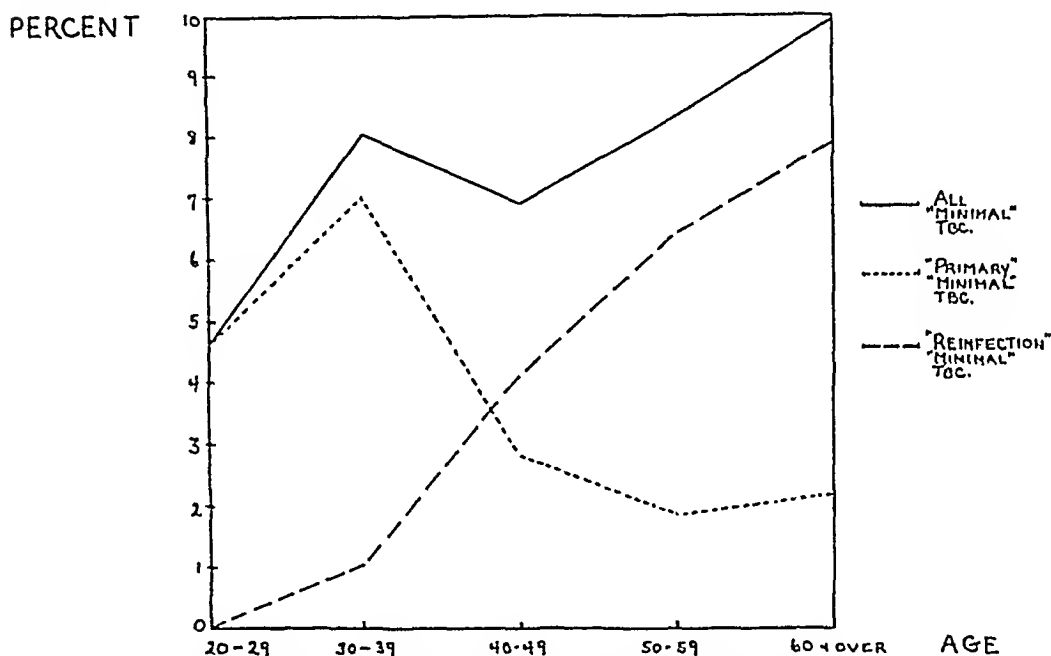
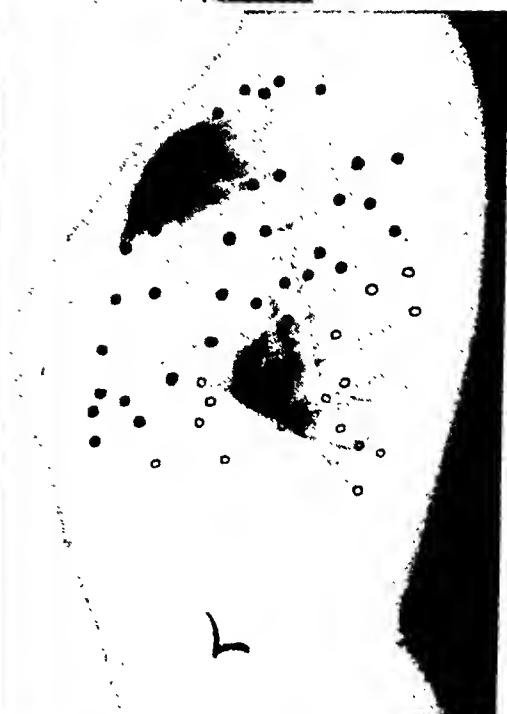
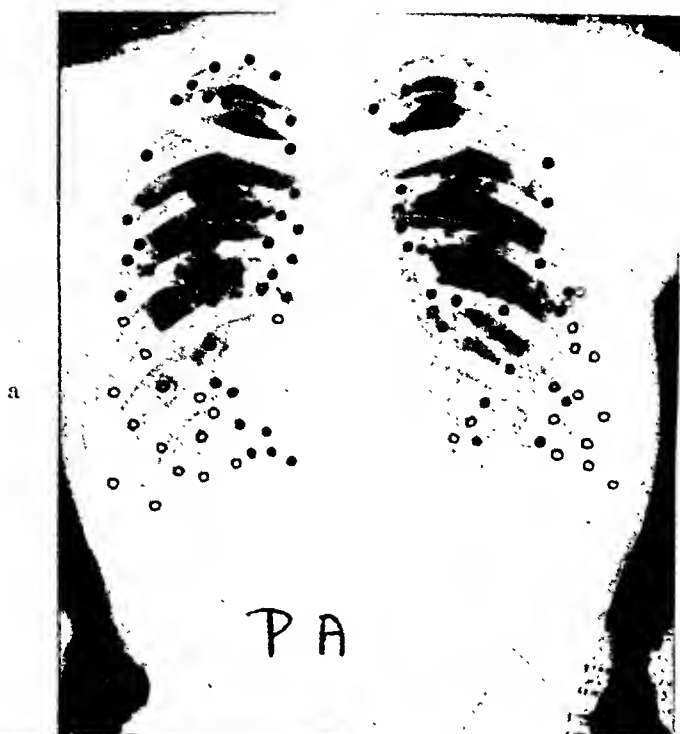


FIG. 1. Percentage of minimal, primary and reinfection pulmonary tuberculosis in different age groups (1,225 necropsies, deaths sudden and unexpected).

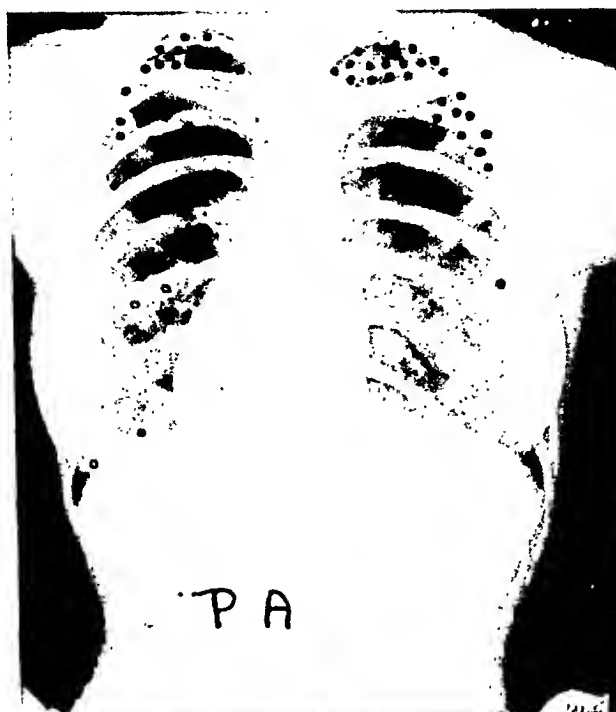
the problem of reinfection disease assumes added significance because there are more deaths from tuberculosis in persons beyond middle age than in young adults, and in the older persons the greater number of deaths occur in white males.

Single discrete roentgenographic shadows of calcium density, commonly interpreted as healed primary or Ghon foci, are observed more often in the lower half of the lung field, whereas the shadows of early progressive pulmonary tuberculosis usually are seen in the upper third of the lung field. Roentgenograms of the persons included in this study were not taken. In every case, however, the location of the lesions was recorded carefully on a diagram of the lung. To determine whether the lesions found would conform in their distribution to the well known roentgenographic pattern, the lesions of each group were assembled on postero-anterior, right and left lateral roentgenograms of



FIGS. 2, 3 AND 4. Relative location of the lesions discussed in the text. A solid dot represents a lesion in an upper lobe; a circle, a lesion in a lower lobe; and a circle with a bar, a lesion in the right middle lobe. PA = postero-anterior; R = right lateral; and L = left lateral roentgenogram.

FIG. 2, a, b, c. Show the location of the calcified parenchymal foci in 105 individuals with a single primary complex.



a



b



c

FIG. 3, a, b, c. Show the location of the minimal lesions in 55 individuals with reinfection tuberculosis.

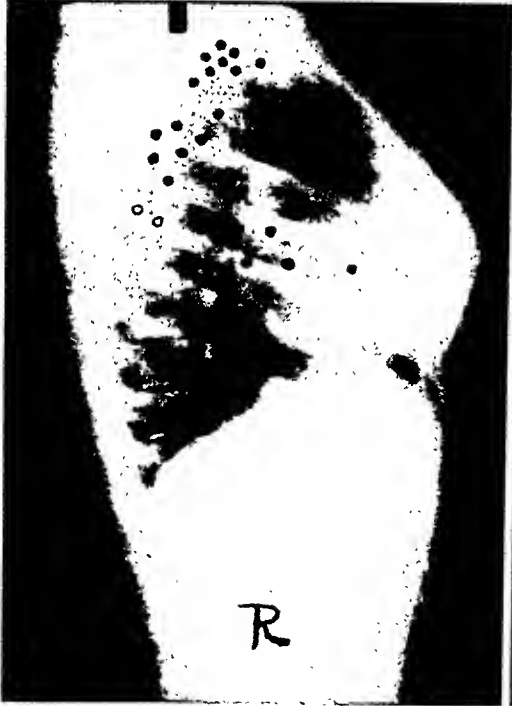
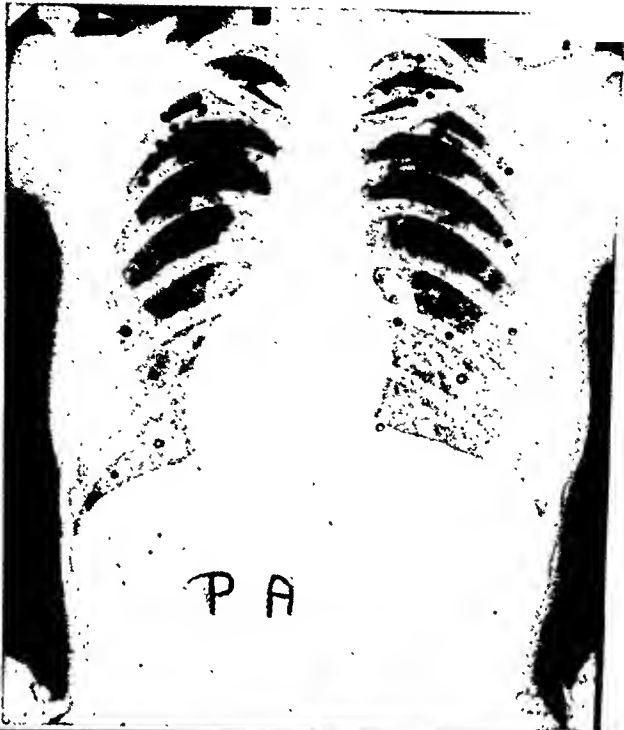


FIG. 4, a, b, c. Show the location of the minimal lesions in 41 individuals with primary tuberculosis.

normal chests. Figures 2, 3, and 4 show the distribution pattern of the parenchymal lesion in the calcified *primary complex*, the *primary* and the *reinfection* groups, respectively.

The scatter pattern of the calcified parenchymal primary foci (figure 2) agrees with the known facts on the subject and is one consistent with a chance distribution of an air-borne infection. Eighty-five per cent of the foci were within 1 cm. of the pleura, two-thirds were in the lower half of the lung field, and only 12 per cent were supraclavicular in location. The lesions were in the right lung in 51 persons, in the left lung in 54, in upper lobes in 42, in lower lobes in 56 and in the right middle lobe in 7. One-fifth of the foci were near the mesial surfaces of lungs in a location such that the shadows would appear in the hilar region in postero-anterior roentgenograms and, in this position, they might readily and erroneously be interpreted as calcific hilar lymph nodes. A similar situation may occur in lateral roentgenograms.

In the reinfection group (figure 3) the right lung was involved in 24 persons, the left lung in 21, and both lungs in 10. The lesions were located in the upper half of pulmonary lobes in 62 (93.9 per cent) instances and in lower lobes in 7 (12.7 per cent) persons. The lesions were supraclavicular in position in 31 (46.9 per cent) and infraclavicular in 23 (34.8 per cent) instances. Three-fourths of the lesions were located in the dorsal portion of the upper half of pulmonary lobes. The primary complex was in the intestine in 7 persons and a reinfection complex was observed in 13 (23.6 per cent) persons.

In the primary group of minimal extent (figure 4), the right lung was the seat of disease in 19, the left lung in 14 and both lungs in 8 persons. The lesions were located in the upper half of the pulmonary lobes in 42 (85.7 per cent) instances and in the dorsal part of these lobes in 35 (71.4 per cent) instances. Thirty-two (65.3 per cent) of the 49 areas of disease were located above the level of the second costochondral junction with 14 (28.5 per cent) supraclavicular and 18 (36.7 per cent) infraclavicular in position. The lesion was in lower lobes in 7 and in the right middle lobe in 3 persons.

A comparison of the two groups of minimal tuberculosis reveals a greater scatter of lesions in the primary group. There is a tendency, however, for the disease to be located in the same areas of lung tissue in both groups. It is evident that, in an individual case, differentiation between primary and reinfection disease by the location of the lesion is not possible.

The predominant characteristic of the lesions in the minimal groups are presented in relation to age in table 2. In this series there was no entire lesion in which exudation without caseation was found. In some the endobronchial metastases did not appear necrotic, but in these lesions caseation was present and was considered the chief characteristic. Primary and reinfection groups both contain lesions that have the same characteristic features although the proportional distribution within age groups shows considerable difference. In persons less than 40 years of age, 9 of 10 caseous lesions were primary in type; and in persons over 40 years of age, 10 or 13 caseous lesions were reinfection in type. Other proportional differences are present in the table. Only 23 (23.9



per cent) of the foci were caseous, of fairly recent origin, and all of the remaining foci exhibited an attempt at repair of the lesion. It would appear that, taken as a whole, the individuals with minimal pulmonary tuberculosis had a certain degree of resistance, although only 13 (13.8 per cent) revealed a completely healed lesion. There were no macroscopic or histologic characteristics of the parenchymal lesions that allowed a clear-cut distinction between primary and reinfection disease.

TABLE 2

*Dominant pathologic features of minimal pulmonary tuberculosis in relation to age and primary or reinfection disease*

| AGE        | TOTAL     |                              |                                  | DOMINANT FEATURE OF LESIONS |                              |                                  |               |                              |                                  |                      |                              |                                  |                |                              |                                  |
|------------|-----------|------------------------------|----------------------------------|-----------------------------|------------------------------|----------------------------------|---------------|------------------------------|----------------------------------|----------------------|------------------------------|----------------------------------|----------------|------------------------------|----------------------------------|
|            |           |                              |                                  | Caseous                     |                              |                                  | Fibro-caseous |                              |                                  | Fibro-caseo-calcific |                              |                                  | Fibro-calcific |                              |                                  |
|            | All cases | Primary minimal tuberculosis | Reinfection minimal tuberculosis | All cases                   | Primary minimal tuberculosis | Reinfection minimal tuberculosis | All cases     | Primary minimal tuberculosis | Reinfection minimal tuberculosis | All cases            | Primary minimal tuberculosis | Reinfection minimal tuberculosis | All cases      | Primary minimal tuberculosis | Reinfection minimal tuberculosis |
|            |           |                              |                                  |                             |                              |                                  |               |                              |                                  |                      |                              |                                  |                |                              |                                  |
| All ages.. | 96        | 41                           | 55                               | 23                          | 12                           | 11                               | 43            | 14                           | 29                               | 17                   | 7                            | 10                               | 13             | 8                            | 5                                |
| 20 to 39.. | 23        | 21                           | 2                                | 10                          | 9                            | 1                                | 7             | 7                            | —                                | 5                    | 4                            | 1                                | 1              | 1                            | —                                |
| 40 to 59.. | 43        | 13                           | 30                               | 9                           | 3                            | 6                                | 22            | 4                            | 18                               | 8                    | 2                            | 6                                | 4              | 4                            | —                                |
| 60+.....   | 30        | 7                            | 23                               | 4                           | —                            | 4                                | 14            | 3                            | 11                               | 4                    | 1                            | 3                                | 8              | 3                            | 5                                |

TABLE 3

*Age distribution of primary and reinfection disease in minimal tuberculosis and in deaths from tuberculosis*

| TYPE OF DISEASE  | DEAD FROM TUBERCULOSIS |              |          |         |          | MINIMAL TUBERCULOSIS |              |          |         |          |
|------------------|------------------------|--------------|----------|---------|----------|----------------------|--------------|----------|---------|----------|
|                  | All cases              | Age in years |          |         |          | All cases            | Age in years |          |         |          |
|                  |                        | Under 40     |          | Over 40 |          |                      | Under 40     |          | Over 40 |          |
|                  |                        | Number       | Per cent | Number  | Per cent |                      | Number       | Per cent | Number  | Per cent |
| Total.....       | 77                     | 34           | 44.2     | 43      | 55.8     | 96                   | 23           | 23.9     | 73      | 76.1     |
| Primary.....     | 34                     | 27           | 79.4     | 7       | 20.6     | 41                   | 21           | 51.2     | 20      | 48.8     |
| Reinfection..... | 43                     | 7            | 16.3     | 36      | 83.7     | 55                   | 2            | 3.6      | 53      | 96.4     |

In a previous study (9) of 100 persons dead from tuberculosis, 77 were regarded as representing clearly either primary or reinfection disease, with the type indeterminate in 23. In the light of the data on tuberculosis of minimal extent observed in cases of sudden and unexpected death, the protocols of those dead from primary or reinfection disease have been re-examined. A comparison of the groups of minimal tuberculosis with the group dead from tuberculosis relative to age distribution is presented in table 3. The age distribution of the reinfection type is strikingly alike and of the primary type is dissimilar in the two groups. In the primary group the difference may be due to the fact that 70

per cent of minimal cases had lesions consistent with an infection of some duration. The data in this table indicate that primary and reinfection tuberculosis occur predominately in different age groups regardless of whether the disease is of minimal extent or is the cause of death.

Macroscopic evidence of a generalized disease in the two groups is shown in table 4. There is a striking difference between primary and reinfection disease in both groups.

The predominant feature of the disease in relation to location in pulmonary lobes in the entire group of minimal cases is presented in table 5. Eighty-eight per cent of all lesions were located in the upper half of pulmonary lobes.

TABLE 4

*Macroscopic evidence of tuberculosis in abdominal organs in primary and reinfection disease, minimal tuberculosis and deaths from tuberculosis*

| TYPE OF DISEASE  | DEAD FROM TUBERCULOSIS |                         |          | MINIMAL TUBERCULOSIS |                         |          |
|------------------|------------------------|-------------------------|----------|----------------------|-------------------------|----------|
|                  | All cases              | TB. in abdominal organs |          | All cases            | TB. in abdominal organs |          |
|                  |                        | Number                  | Per cent |                      | Number                  | Per cent |
| Total.....       | 34                     | 26                      | 76.4     | 41                   | 11                      | 26.8     |
| Primary.....     | 77                     | 38                      | 49.3     | 96                   | 12                      | 12.5     |
| Reinfection..... | 43                     | 12                      | 27.9     | 55                   | 1                       | 3.6      |

TABLE 5

*Areas of minimal pulmonary tuberculosis. Comparison with regard to location in lobes of lung and dominant feature of lesions*

| LOCATION OF LESIONS<br>IN LOBES | NUMBER<br>OF AREAS | DOMINANT FEATURE OF LESIONS |          |               |          |                      |          |                |          |
|---------------------------------|--------------------|-----------------------------|----------|---------------|----------|----------------------|----------|----------------|----------|
|                                 |                    | Caseous                     |          | Fibro-caseous |          | Fibro-caseo-calcific |          | Fibro-calcific |          |
|                                 |                    | Number                      | Per cent | Number        | Per cent | Number               | Per cent | Number         | Per cent |
| Total.....                      | 115                | 29                          | 25.2     | 53            | 46.1     | 19                   | 16.5     | 14             | 12.1     |
| Upper half.....                 | 101                | 26                          | 25.7     | 50            | 49.5     | 17                   | 16.8     | 8              | 7.9      |
| Lower half.....                 | 14                 | 3                           | 21.4     | 3             | 21.4     | 2                    | 14.4     | 6              | 42.8     |

Lesions having similar characteristics were found in both halves of lobes. Proportionally, however, there were more healed lesions in the lower half of lobes.

It is neither feasible nor necessary to illustrate the anatomic and histological character of all of the minimal tuberculous lesions. The illustrations have been selected to show representative primary and reinfection lesions in persons of different age; they show a cross section of the entire area of the lesion and the explanations accompanying the illustrations make further comment here unnecessary.

#### DISCUSSION

When tuberculous lesions of minimal extent are observed at necropsy, they do not present a uniform pathological picture, nor are they early or young in

terms of the pathogenesis of the disease. Eighty-seven per cent of the persons in the minimal groups analyzed in this presentation harbored unhealed disease, as shown by the presence of necrotic (caseous) foci and endobronchial metastases. Not a single case was observed in the entire series of necropsies of a tuberculous lesion of minimal extent in which the entire focus was exudative, hence non-necrotic, like the areas of acute, nontuberculous lobular pneumonia so commonly observed at necropsy. In a search of the literature, no case of purely exudative minimal pulmonary tuberculosis has been found. From a considerable experience in experimentally produced tuberculosis, in comparative pathology and in necropsy observation on human beings, the writer believes: that all foci of air-borne tuberculous infection begin as microscopical foci of pneumonia, similar to the lesion reported by Pagel (10); that the area of pneumonia enlarges through the accumulation of leucocytes from the circulating blood; and that, by the time the lesion attains a size sufficient to be recognized macroscopically, necrosis (caseation) of the original focus has already occurred and in many instances local endobronchial metastases have also developed. The length of time required to reach this stage in man cannot be determined, but in experimental animals a few weeks to a few months are required for an area of disease to develop that is comparable to minimal pulmonary tuberculosis in man. No evidence was found at necropsy to support the thesis that minimal tuberculosis arises as a prompt reaction to a massive air-borne infection. Evidence is also lacking to support the thesis that disease of this extent has its origin either from a hematogenous or from a lympho-hematogenous source. All of the data obtained in the examination of the series of 1,225 necropsies indicate that, when minimal pulmonary tuberculosis is first demonstrable in roentgenograms, caseation of an area of tuberculous lobular pneumonia is present and local endobronchial metastases have already occurred in a high percentage of the cases.

In selecting the cases of minimal disease, only those that had a lesion of a size thought to be sufficient to cast a roentgenographic shadow were chosen for study. Whether the smallest lesions that were included would have been demonstrable cannot be determined as roentgenograms were not available. The shadows that might have been observed, had roentgenograms been obtained, however, would have varied in density, location, extent and configuration. In 30 individuals shadows of calcium density would have been present, and in 17 of these the lesions also contained unorganized foci of caseation. This situation indicates that caution should be exercised in the diagnosis of healed tuberculosis when shadows which exhibit scattered foci of calcium density are observed in the upper third of the lung field.

Two schools of thought relative to the pathogenesis of progressive pulmonary tuberculosis in adults have existed for many years. One school supports the thesis that the primary infection acquired in childhood lies dormant for unknown reasons until adolescence, when it becomes a progressive pulmonary disease (endogenous reinfection tuberculosis) with the site from which the disease is spread being caseous tuberculous lymph nodes (lympho-hematogenous tuberculosis). The second school of thought supports the thesis that the primary

infection acquired in childhood is an innocuous disease that heals completely. During its course, however, an "allergic" soil is created and the stage is set for the development of a progressive disease, if the individual becomes infected a second time (exogenous reinfection tuberculosis). Both schools agree that progressive pulmonary tuberculosis (phtthisis) has its inception in the upper third of the lung field, some maintaining that it begins in the apex, some that its origin is subapical. Both schools consider that the allergic soil enhances the development of the progressive disease.

The data presented in this paper show that calcified primary parenchymal lesions, even when there is only one in a pair of lungs, have a pattern consistent with a chance distribution of an air-borne infection. In this group evidence of lympho-hematogenous disease was lacking and evidence of hematogenous dissemination was found in only 8.5 per cent of the cases. The disease was strictly limited to the parenchymal focus and the lymph nodes in the path of drainage in 92 per cent of the individuals. All of the parenchymal foci were completely calcific and in only 4 individuals were the lymph nodes caseo-calcific, indicative of a failure of complete healing. No cultures were made of the lesions, but the reports of Opie and Aronson (11), of Sweany (12) and of Feldman (13) indicate that viable bacilli are found infrequently in lesions of this type.

The distribution pattern of the minimal disease was atypical for chance distribution of an air-borne infection for the lesions were predominantly dorsal in position and within the upper half of pulmonary lobes, both apical and subapical in location. The pattern is not one suggestive either of an hematogenous or of a lympho-hematogenous origin of the disease as the lesions were unilateral in 82 per cent of the individuals. Moreover, evidence of tuberculosis in the abdominal organs was observed in only 12 (12.8 per cent) persons, 11 of whom were in the primary group.

These data do not conform to the concepts of either school of thought mentioned above. It does not seem logical that an "allergic" state would make certain areas only of the lung more susceptible to an air-borne infection. It is even more difficult to understand how an "allergic" soil would make these same selective areas of lung tissue so susceptible to an hematogenous or a lympho-hematogenous distribution of tubercle bacilli. The data do indicate that in adults certain areas of pulmonary lobes are especially subject to the development of progressive tuberculosis.

Evidence (14) has been submitted that under certain conditions in both normal and vaccinated, hence "allergic", rabbits, pulmonary tuberculosis produced by the intravenous inoculation of bacilli, develops into bilateral caseous cavitating disease only in the dorsal and caudal areas of the lungs. It was further observed that the location of this type of disease could be changed by forcing animals to stay in an upright rather than in a normal horizontal position. It has also been reported (15) that caseous cavitating pulmonary tuberculosis in cattle, an air-borne infection, usually was unilateral and predominantly located in the same area of lung as had been observed in rabbits with a blood-borne infection. These observations suggest that posture is a factor of more importance in the

development of localized progressive pulmonary tuberculosis than the source of the infection, the type of infection, *i.e.*, primary or reinfection, or the initial dosage of bacilli at the site of infection.

In man, posture cannot be the only factor in the pathogenesis of progressive pulmonary tuberculosis, for calcified parenchymal primary lesions occasionally are found in the areas in which progressive disease is apt to develop. Dock (16) has suggested that gravity and arterial blood flow may be decisive factors. Any explanation that may be suggested to account for the phenomenon of phthisis must be applicable primarily to the dorsal and cephalic portion of *all* pulmonary lobes.

To recapitulate, the pattern of minimal pulmonary tuberculosis suggests: that certain areas of the lung parenchyma are subject to the development of progressive disease, although the reasons for this selectivity are not understood; that evidence to support an hematogenous or a lympho-hematogenous origin of the lesions is lacking; and that lesions may ensue from a chance lodgment of air-borne bacilli in a vulnerable area either in a normal or in an altered (allergic) lung parenchyma.

In a comparison of the group of minimal disease with a group of individuals who died from tuberculosis, it was found that in both groups primary disease was predominant in persons less than 40 years of age and reinfection disease was ascendant in persons over 40 years of age. The average age of the primary group of fatal cases was 34 years and of the reinfection group, 52 years. In the group of fatal cases primary disease accounted for 79.4 per cent of the deaths of persons under 40 years of age and reinfection disease for 83.7 per cent of the deaths of individuals over 40 years of age. In the group of minimal tuberculosis, the disease was primary in 91 per cent of the persons under 40 years of age and was reinfection in 72.6 per cent of individuals over 40 years of age. In this respect there is a striking similarity relative to primary and reinfection disease in the two groups.

A significant difference between the primary and the reinfection groups in both minimal and fatal tuberculosis is the greater frequency of macroscopic evidence of hematogenous dissemination of the disease in the primary group. This suggests either that these individuals are less successful in preventing the invasion of the bacilli into the blood stream or that they have greater difficulty in destroying the bacilli once they have gained entrance to the blood stream. In either event it seems logical that individuals with progressive primary tuberculosis would tend to develop extrapulmonary metastases, *i.e.*, renal, bone, meningeal, et cetera, much more often than individuals with reinfection tuberculosis. This should receive due consideration in the management of young adults with tuberculosis, for it is in this age group that primary disease appears to be predominant.

In the various papers of Terplan (4) there are 87 well documented cases of reinfection tuberculosis with 85 per cent of the individuals over 40 years of age, and 31 cases of recent (caseous) primary lesions with 68 per cent less than 40 years of age. It is uncertain whether all of these cases would conform to the

criteria used in this paper for minimal pulmonary tuberculosis. Considering the difference in the source of material and in locale, there is a significant similarity between Terplan's and the present observations.

The difference in pattern of pulmonary tuberculosis in the child and in the adult has led to the use of the term of "adult type" of tuberculosis and it is generally thought that the difference is due to reinfection. The basis for this concept is that: (a) a high proportion of adults in large urban areas react to tuberculin, and (b) in the majority of necropsies on adults, calcific tuberculous foci may be found in the lungs. The clinical studies of Amberson and Riggins (17), of Badger, *et al.* (18), of Malmros and Hedvall (19), and others have revealed roentgenographic evidence of minimal pulmonary tuberculosis more often in persons who recently became reactors to tuberculin than in those who had been known to be reactors for some time. In these persons the disease develops in the area of lung tissue in which only reinfection disease is supposed to develop. Homburg (20) quotes Uehlinger to the effect that, in 72 necropsies on Swiss soldiers who died from tuberculosis in 1939-1941, 60 had the characteristics of primary disease. The data presented in this paper show that minimal pulmonary tuberculosis in young adults is largely a primary disease. The writer agrees with Malmros (21) that "the frequently employed terms 'reinfection' and 'reinfection type' are misleading," insofar as they are applicable to a clinical interpretation. Reinfection disease is a reality that ascends with increase in age of a population. There is sound ground in pathology for the terms primary and reinfection types, but it is not possible to differentiate the two conditions from the location or characteristics of roentgenographic shadows.

It is much more difficult to discover evidence of tuberculosis in lymph nodes in adults than in children. Meticulous examination of lymph nodes at necropsy on adults is arduous, but it is mandatory if precise information is to be obtained. All lymph nodes draining the pulmonary parenchyma and the ileum, caecum and ascending colon must be examined, for in a high percentage of cases they will contain whatever evidence of tuberculosis there may be in these structures. It was not uncommon in the examination of the series of necropsies on which this paper is based to find a single lymph node of normal size and normal texture on palpation that contained a single focus of caseation or of calcification two millimeters or less in diameter.

#### *General Considerations*

All persons who come under the jurisdiction of the Office of the Medical Examiner of the Borough of Manhattan, and on whom necropsies are performed, are sent to the morgue at Bellevue Hospital where postmortem examinations are conducted on all individuals who died from violence or under obscure circumstances. These persons are from all parts of the borough, various economic levels, different races, all ages and both sexes, and represent a small but representative cross section of the population. This was the source from which the data presented in this paper were collected. In the study the only selectivity exercised was the rejection of individuals who had extensive pulmonary disease, other

than tuberculosis, with a loss of less than 5 per cent for this reason. The only limiting factor in the number of individuals examined was that a thorough search was made in each case for evidence of tuberculous infection, and as a result only about one-third of the persons could be investigated.

The data presented are factual and concern the problem of the epidemiology and the control of tuberculosis in a congested urban area. Pulmonary tuberculosis of minimal extent was found in 7.8 per cent of adults over 20 years of age, with an incidence of 4.7 per cent between the ages of 20 to 29 years and 9.9 per cent in persons over 60 years of age. Lesions in different phases of development were present in all age groups and were in an unhealed state in 86.5 per cent of the cases. The lesions represented primary disease twice as often in the Negro as in the white race and reinfection disease three times as often in the white as in the Negro race, with the white male surpassing the white female 3 to 1. The writer believes that primary tuberculosis causes death much more often in the Negro than in the white adult, and that one reason why progressive reinfection tuberculosis predominates in the white male in contrast to the white female over 40 years of age is because his mode of life favors a more frequent exposure to infection.

The importance placed upon mass roentgenographic surveys of the chest reflects the urge to discover tuberculous disease early. In this connection, familiarity with the distribution pattern of the lesions of minimal pulmonary tuberculosis, as well as the pathologic significance of roentgenographic shadows in the upper third of the lung field, is important. In this part of the chest small parenchymal lesions not infrequently are located in such a position that the heavy structures of the shoulder girdle and the spinal muscles render their demonstration difficult. This can be appreciated from a study of figures 3 and 4.

The disposal of the cases of minimal pulmonary tuberculosis found in mass surveys presents a problem of major importance. Hilleboe (22) has suggested that cases of this type need not be placed under hospital supervision unless tubercle bacilli have been demonstrated in sputum or gastric contents, a procedure that requires many laboratory tests in a majority of cases. This is the view of the epidemiologist and of many private physicians interested in mass surveys in which a majority of the cases discovered have lesions of minimal extent and in which a major problem is the disposal of these cases. Amberson (23) takes issue with this view and recommends that adults, especially if they are young, with disease of minimal extent be given the benefit of careful hospital supervision. This is the view of the clinician with wide experience in the treatment of tuberculous patients. The data presented in this paper favor Amberson rather than Hilleboe. Tuberculosis is predominately a primary disease in young adults and extrapulmonary lesions are more likely to develop than if it were a reinfection disease. Tuberculous lesions of minimal extent persist in an unhealed state for a long time even when the individual is clinically well and in no need of hospital care. All persons with persistent roentgenographic shadows in the upper lung field should have roentgenograms taken periodically regardless of their clinical status or the extent and character of the shadows. An expert roentgenologist, from his own experience, may decide whether an individual is

in need of immediate hospital supervision but he cannot render an accurate diagnosis of "healed", "obsolete" or "of no clinical significance" in any given patient.

Pinner (24) observes "that the pathogenesis of tuberculosis is a problem that can never be solved by the pathologist or the experimentalist alone; but only by the careful integration of pathological, experimental, clinico-roentgenological and epidemiological methods." The writer agrees with the second part of the statement but would reword the first part by replacing "the pathologist or the experimentalist" with "the epidemiologist or the clinician." The reason for this rewording is that in this country tuberculin, statistical, and mass roentgenographic surveys, as well as extensive clinical experience, have received far greater attention, encouragement and support than have careful, well-documented studies of available necropsy material and of animal experimentation. There is a quite prevalent attitude that what is observed in an animal cannot be applied to man and that what is observed at necropsy concerns little the problems of the living. This attitude hardly seems justified.

In another place Pinner (24) states that "necropsy findings in persons who never developed progressive tuberculosis may not be the proper material for studies on the pathogenesis of clinical tuberculosis." Clinical tuberculosis, the treatment of those who are ill from tuberculosis, has its roots in pathology, and it is unfortunate that the subclinical lesions, not infrequently encountered at necropsy on persons dead from causes other than tuberculosis, have received such scant attention. In this country few pathologists have a special interest in tuberculosis and still fewer realize the confused thought relative to the pathogenesis of the disease. There is a wealth of information that could become available from routine necropsy services if time and care were used to document carefully all discoverable evidence of tuberculous infection. This will not be done unless the epidemiologist, the statistician, and the clinician help to create a real interest in and avail themselves of such recordings. In this country it is rare to find such well-documented observations on tuberculosis, observed in persons dead from causes other than tuberculosis, as the reports of Terplan (4), a former pupil of Ghon. It is not to be anticipated that the observations on routine necropsies in one part of the country should apply to the country as a whole; nor should the necropsy data from older civilizations, such as those in Europe, be applied uncritically to the problem of tuberculosis in the United States. In this respect the writer agrees with Pinner (24) that "Tuberculosis changes with time and place. For this reason, every country and possibly even smaller subdivisions must investigate their local epidemiological conditions; none can accept, without proof, the findings in some other regions."

The resurgence of interest in prophylactic vaccination against tuberculous infection through the use of BCG is due, in large part, to an appreciation that progressive tuberculosis in young adults often is a primary disease. It is essential that all useful procedures be employed to combat the disease. In the use of prophylactic vaccination, however, great care must be exercised to avoid the concept that the procedure will afford a quick and easy solution to the problem. In this connection it is paramount that the *pathogenesis of tuberculosis as a*



*whole* be kept in mind at all times. It has long been known, from animal experiments, that prophylactic vaccination with BCG increases the resistance to tuberculous infection and it is also well known that a natural vaccination in man fails to give complete protection against a subsequent tuberculous infection. Clinical studies have shown that only a small percentage of young adults who acquire a primary infection develop a progressive disease and the data presented in this paper indicate that progressive disease in older adults occurs in large part in persons who have completely healed a previous infection. There are many more deaths from reinfection than from primary tuberculosis and, in addition, there are many more old than young adults who harbor lesions from which tubercle bacilli may be scattered in the air. Even under the most favorable circumstances a single prophylactic vaccination in youth logically would fail to solve the problem in the older persons in a population. The vaccination of a whole population from time to time might mitigate the problem, but there is reason to believe that such a procedure would not lead to an eradication of the disease. The best procedure would be to protect the youth from ever becoming infected, and to accomplish this end it is paramount that a permanent solution be found for complete control of tuberculosis in persons beyond the age of 40 years.

#### SUMMARY

1. An analysis is presented of 96 persons with minimal pulmonary tuberculosis, obtained from necropsy of 1,225 cases of sudden and unexpected death.

2. The disease represented a *primary* infection in 42.7 per cent and a *reinfection* in 57.3 per cent.

3. Primary disease was 2.7 times more common in persons less than 40 than in those over 40 years of age.

4. Reinfection disease was 10 times more common in persons over 40 than in those less than 40 years of age.

5. Of 23 persons less than 40 years of age, the minimal disease was primary in 91 per cent.

6. Of 73 persons over 40 years of age, the minimal disease was a reinfection in 72.6 per cent.

7. Macroscopic evidence of tuberculous lesions in one or more abdominal viscera was found 7 times more often in the primary than in the reinfection group. This suggests that extrapulmonary tuberculosis may be expected more often in persons with primary than with reinfection disease. This possibility should be carefully considered when the medical regimen for a patient is under consideration.

8. The pattern of distribution and the pathologic characteristics of the disease are similar for both primary and reinfection minimal disease. This indicates that it is not possible from roentgenographic shadows to differentiate between the two conditions.

9. When considered on the basis of pathogenesis, primary and reinfection progressive disease are realities. They present major problems in different age groups of a population, although there is an overlapping to a certain degree.

10. In the group of 96 persons analyzed, only 13 (13.8 per cent) presented a completely healed disease. Complete healing was found in only 7.9 per cent of the foci in upper portions of pulmonary lobes, whereas 42.8 per cent of the lesions in the lower half of the pulmonary lobes were healed.

11. Shadows caused by tuberculous lesions in the upper lung fields should not be interpreted as "healed" if there are scattered small calcific densities, for the majority of such lesions also contain unorganized necrotic (caseous) areas of tuberculous pneumonia.

12. More thorough investigations of routine necropsy material relative to the pathogenesis of tuberculosis are needed. A program of this type deserves support and encouragement from epidemiologists, statisticians, pathologists, and clinicians alike.

#### SUMARIO

##### *La Patogenia de la Tuberculosis Pulmonar Mínima*

1. Este análisis abarca 96 casos de tuberculosis pulmonar mínima, tomados de las autopsias de 1,225 casos de muerte súbita e inesperada.

2. La enfermedad representó infección *primaria* en 42.7 por ciento y reinfección en 57.3 por ciento.

3. La afección primaria fué 2.7 veces más frecuente en las personas de menos de 40 años que en las de más de 40 años de edad.

4. La enfermedad tipo reinfección fué 10 veces más frecuente en las personas de más de 40 años que en las de menos de 40 años de edad.

5. Entre 23 personas de menos de 40 años, la tuberculosis mínima fué primaria en 91 por ciento.

6. Entre 73 personas de más de 40 años, la tuberculosis mínima fué de tipo reinfección en 72.6 por ciento.

7. Los signos macroscópicos de lesiones tuberculosas en una o más vísceras abdominales fueron 7 veces más frecuentes en el grupo primario que en el de reinfección, lo cual sugiere que cabe esperar tuberculosis extrapulmonar más a menudo en los enfermos de tipo primario que en los de tipo reinfección. Esta posibilidad debe recibir cuidadosa atención al estudiar el régimen médico para un enfermo.

8. El molde de distribución y las características patológicas son semejantes en la enfermedad mínima tanto tipo primario como reinfección, lo cual indica que no es posible diferenciar los dos estados por las sombras radiográficas.

9. Considerados a base de la patogenia, los tipos primario y reinfección de la enfermedad evolutiva constituyen realidades, planteando problemas de primera magnitud en diversos grupos etarios de la población, aunque se sobreponen hasta cierto punto.

10. En el grupo de 96 personas analizadas, sólo 13 (13.8 por ciento) presentaban enfermedad completamente curada. Sólo se encontró cicatrización completa en 7.9 por ciento de los focos de las porciones superiores de los lóbulos pulmonares, comparado con 42.8 por ciento en las lesiones de la mitad inferior de los lóbulos.

11. No deben interpretarse como "cicatrizadas" las sombras ocasionadas por

lesiones tuberculosas en los campos pulmonares superiores si hay pequeñas calcificaciones espesas esparcidas, pues la mayoría de esas lesiones también contienen zonas necrosadas (caseosas) no organizadas de neumonía tuberculosa.

12. Necesítanse investigaciones más minuciosas del material autopsico corriente en relación con la patogenia de la tuberculosis. Una obra de esta índole merece apoyo y aliento de parte por igual de los epidemiólogos, estadísticos, patólogos y clínicos.

#### PLATE I (Figures 1 to 10)

The photomicrographs represent the actual size of a crosssection of each minimal lesion and each lesion is no larger in any dimension than the section shown.

FIG. 1. (Negro female, age 35 years). Acute alcoholic death. Primary lesion.

This individual had three separate primary foci with the lymph nodes draining each focus showing considerable necrotic tuberculosis. These lesions are listed as caseous in the tables as there was no evidence of organization. There were several 2 to 3 mm. necrotic tuberculous foci in the spleen, liver, kidneys and adrenals.

A. This lesion was infraclavicular, dorsal and lateral in position in the left upper lobe. The central necrotic core was soft and hemorrhagic. Endobronchial metastases occupied a lobule of the lung distal to the necrotic core and smaller foci were present in the lung parenchyma outside of this area. No adhesions were present.

B. This lesion was dorsal in position in the apex of the left lower lobe and was nearer the mesial than the lateral surface. This location would place the focus in the hilar region in a postero-anterior roentgenogram of the chest. The lesion was soft and caseous and small bronchogenic metastases were present in the adjacent lung parenchyma. No adhesions were present.

C. This lesion was in the right upper lobe 2 cm. from the extreme apex, lateral and about midway between the dorsal and ventral surfaces. It was located in a region that is difficult to visualize in a postero-anterior roentgenogram. The lesion is similar to B. Small endobronchial metastases were present at the extreme apex of the lobe.

FIG. 2. (Colored male, age 18 years). Homicidal death. Primary lesion.

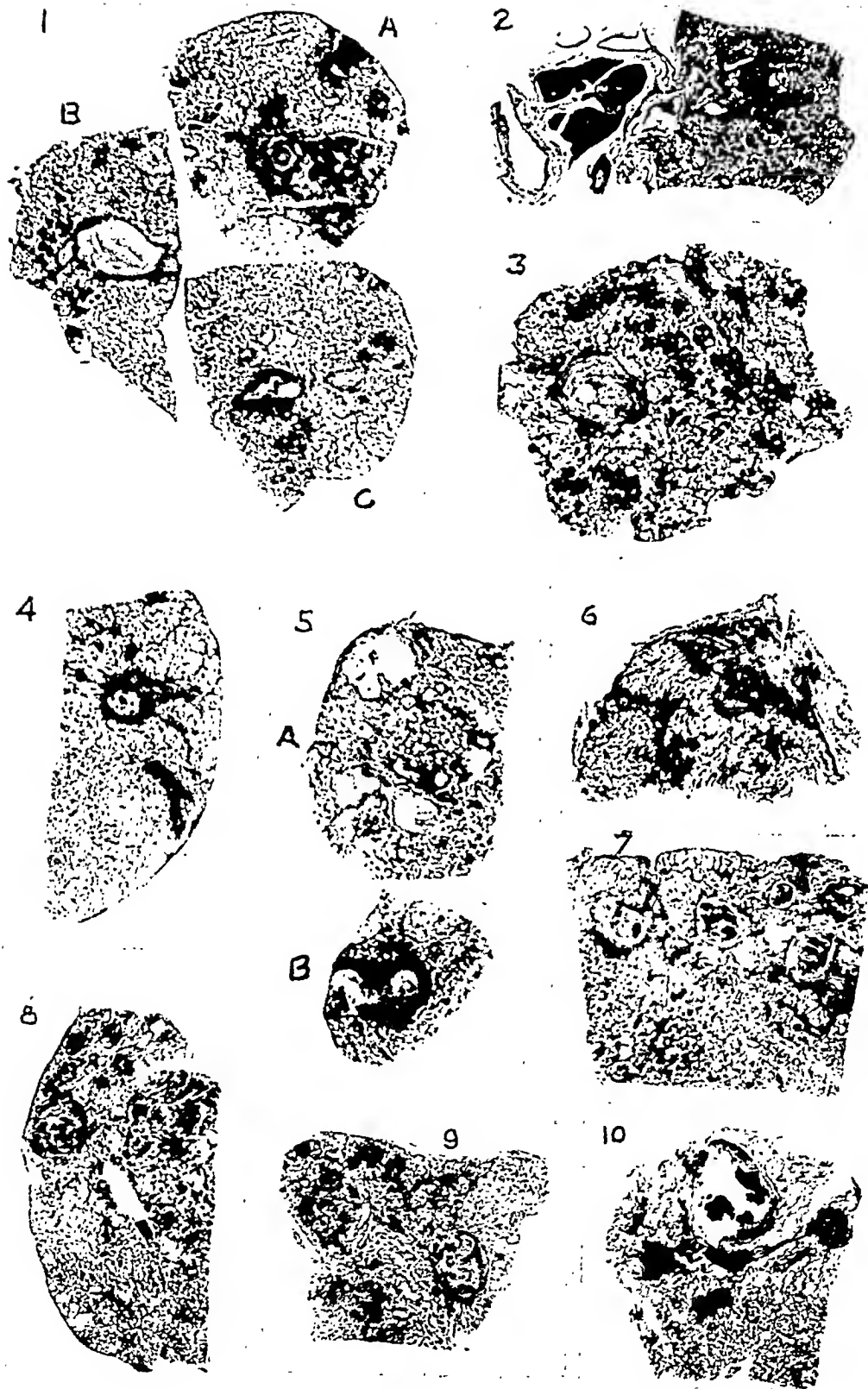
The section is through the hilar region of the right upper lobe and there is a 5 mm. caseous lesion 1 cm. beneath the mesial pleura with a few small endobronchial metastases in the adjacent lung parenchyma. The lymph nodes present in the section of tissue were not enlarged and were normal on palpation. Section showed a number of separate small caseous tuberculous foci in three lymph nodes. It required a thorough search to locate the parenchymal focus because of its unusual location. That a parenchymal lesion was probably present was suggested when the lesions in the lymph nodes were discovered. The parenchymal and lymph node lesions represent a primary complex. This individual was not included in the group discussed in this paper because of the small size of the lesion and because it would probably not be detectable in a roentgenogram on account of its location. Lesions of this character, usually smaller in size, that were located in areas similar to those in persons included in the study were observed in a number of individuals but none of them were included in the study.

FIG. 3. (White male, age 45 years). Traumatic death. Reinfection lesion.

The lesion was located in a dorsolateral and infraclavicular area of the left upper lobe. The supraclavicular area of both lungs was free from lesions. The large caseous focus was rather soft and partly liquefied with a small fibrotic capsule. The surrounding endobronchial metastases varied considerably in appearance. Some were caseous while others were "classical" tubercles. No pleural adhesions were present. The healed primary complex was in the right lower lobe. This lesion is classed as fibro-caseous in the tables.

FIG. 4. (White male, age 55 years). Traumatic death. Reinfection lesion.

The lesion was present in the right upper lobe in a dorsolateral position approximately 3 cm. from the extreme apex. A few cobweb adhesions were present over a small area. A 4 mm. cavity that was partly filled with frank pus was located 1 cm. beneath the pleura.



There were a number of endobronchial metastases present and no evidence of organization of the lesion was found. One healed primary complex was found in the right middle lobe and another in the left lower lobe. The lesion is listed as caseous in the tables.

FIG. 5. (White male, age 50 years). Traumatic death. Reinfection lesion.

A. This lesion involved the apex of the left upper lobe in its dorsal and lateral aspect. A cavity less than 1 cm. in diameter was present just beneath the pleura and a very few fragile adhesions were present over it. The surrounding endobronchial metastases varied in size and for the most part were caseous. No evidence of fibrotic organization was found. The cavity contained a small amount of purulent debris and its wall was made up entirely of necrotic material and inflammatory exudate.

B. This lesion was in the dorsolateral area of the right upper lobe approximately 3 cm. below the extreme apex. The lesion was soft, necrotic and intensely congested in the periphery. Although the focus extended directly to the pleura, there were no adhesions. Because of the excavation in the opposite lung, this lesion is regarded as an endobronchial metastasis.

There were no apical scars. The healed primary complex was present in the right middle lobe. The lesions are listed as caseous in the tables.

FIG. 6. (White male, age 72 years). Traumatic death. Primary lesion.

The lesion was in the dorsal part of the apex of the left upper lobe with this part of the lung firmly adherent to the chest wall. There were considerable dense fibrous tissue and linear fibrotic lesions in the lung tissue. A 4 mm. dense calcific focus was present. The only inflammatory reaction present was small collections of lymphocytes in the scarred areas. The lymph nodes draining this area of lung showed a number of small dense calcified foci and some fibrosis. This is the only evidence of tuberculosis found in this individual. The lesion is listed as fibro-calcific in the tables.

FIG. 7. (White male, age 66 years). Death due to coronary occlusion. Reinfection lesion.

This lesion was present in the right upper lobe in an infra-clavicular dorsolateral location. There were fibrotic, fibrocalcific, fibrocaseous and caseous foci present in the lesion. There were no pleural adhesions. Typical bilateral apical scars were present but no microscopical evidence of tuberculosis was found in them. They were disassociated completely from the tuberculous lesion. The healed primary complex was found in the left upper lobe. The reinfection lesion is listed as fibro-caseo-calcific in the tables.

FIG. 8. (White male, age 36 years). Traumatic death. Primary lesion.

The lesion was present in the right upper lobe at midclavicular level near the ventral surface of the lobe. A small cavity was present in the soft necrotic focus that measured 1 cm. in diameter. A number of small endobronchial metastases were present. There were no adhesions. The lymph nodes draining the area showed several 1 to 2 mm. necrotic tuberculous foci. The lesion is listed as caseous in the tables.

FIG. 9. (Negro male, age 35 years). Death resulted from sickle cell anemia and cardiac hypertrophy and dilatation. Primary lesion.

The lesion was present in the left upper lobe in a dorsolateral infraclavicular location. A soft caseous focus, 8 mm. in diameter, was partly excavated and the lung parenchyma distal to this lesion showed numerous endobronchial metastases. There were no pleural adhesions and no evidence of fibrotic organization was found in the lesion. The lymph nodes draining this portion of the lung were not enlarged and on section showed a number of small necrotic tuberculous foci. The lesion is registered as caseous in the tables.

FIG. 10. (White male, age 66 years). Traumatic death. Reinfection lesion.

The lesion was located in a dorsal position approximately 1 cm. below the extreme apex of the left upper lobe. There were no pleural adhesions. There were fibrotic, fibro-calcific, fibrocaseous and caseous foci in the lesion. The large lesion present in the illustration was so densely calcific that most of the material had to be removed before a section of the tissue could be obtained. There was no definite cavity found in the lesion. The healed primary complex was located in the left lower lobe. The lesion is registered as fibro-caseo-calcific in the tables.

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# MINIMAL PULMONARY TUBERCULOSIS<sup>1</sup>

Its Significance in Relation to the Age of the Patient

ROBERT CHANG

## INTRODUCTION

With the ever increasing utilization of mass and routine chest roentgenography in industries, schools, hospitals, and communities, many more cases of minimal pulmonary tuberculosis have been detected in recent years. While in certain cases the roentgenographic appearance of the lesion permits the diagnosis of active disease, in a considerable proportion, however, such a diagnosis can only be made after prolonged observation. The decision as to which patients should be sent to a sanatorium for observation at the time of the initial diagnosis has always been a difficult one. In the past, many cases of minimal pulmonary tuberculosis have been sent to sanatoriums and discharged as inactive from four to six months later. Others, in contrast, were not hospitalized until the lesion showed evidence of progression. The relation between the potentialities of a minimal lesion and the age of the patient has always been impressive in the writer's experience. The purpose of this article is to study such relationship from different aspects.

## OBSERVATIONS

The present study is based on 164 minimal cases admitted to the Rutland State Sanatorium between 1938 and 1945, inclusive. Patients leaving the sanatorium against advice are excluded. Except for a few cases in which prolonged postsanatorium observation was deemed unnecessary, all the discharged patients have been followed for a minimal period of two years. The 164 patients are divided arbitrarily, according to their ages, into three groups: those below twenty-five years of age; those from twenty-five to thirty-eight inclusive; and those above thirty-eight.

In this study, a lesion was called active when there were demonstrable changes in serial roentgenograms, or when the sputum was positive for tubercle bacilli, or both. It was considered progressive when there was roentgenographic evidence of progression during the period of sanatorium residence. The sputum was termed negative only after failure to demonstrate tubercle bacilli on at least ten cultures of sputum and three guinea pig inoculations of gastric washings.

## *Race and Sex*

There is only one Negro patient in the series. Table 1 demonstrates the preponderance of females in the younger patients.

<sup>1</sup> From the Rutland State Sanatorium, Department of Public Health, Commonwealth of Massachusetts.

*Character of Lesions*

In this study an attempt was made to place all the minimal lesions in three pathological categories: the recent infiltrates; the old fibroid "minimal"; and the mixed, which includes all lesions that could not be placed in the former two categories. There were twenty recent infiltrates in the series, of which 12 were found in patients below twenty-five, 8 in patients between twenty-six and thirty-eight, and none in patients above thirty-eight. There were 103 cases with lesions classified as mixed. These constituted 62.7 per cent of all lesions in the series, 74.7 per cent of all lesions found in patients below twenty-five, 65 per cent of those between twenty-six and thirty-eight, and 41.4 per cent of those above thirty-eight. Of 41 cases of fibroid "minimal," 24 were in patients above thirty-eight, making up 58.6 per cent of all lesions found in that group of patients. Only four cases of fibroid "minimal" were found in those below twenty-five (table 2).

TABLE 1  
*Number of male and female patients in different age groups*

| SEX         | AGE      |          |          |
|-------------|----------|----------|----------|
|             | Below 25 | 25 to 38 | Above 38 |
| Male.....   | 21       | 31       | 22       |
| Female..... | 42       | 29       | 19       |

TABLE 2  
*Number of different types of lesions in different age groups*

|                        | BELOW 25 | 25 TO 38 | ABOVE 38 |
|------------------------|----------|----------|----------|
| Early infiltrates..... | 12       | 8        | 0        |
| Mixed.....             | 47       | 39       | 17       |
| Fibroid "minimal"..... | 4        | 13       | 24       |

It appears safe to conclude that the early infiltrates are chiefly found in young patients; that fibroid "minimal," though not uncommon in young patients, constitutes a large portion of lesions found in the older patients; and that the majority of the latter patients have had tuberculosis long before the time of detection.

*Bacteriological Study of Sputum*

In the series of 119 clinically active cases, 21.8 per cent were positive for tubercle bacilli on smears, 47.9 per cent on cultures only, and 21 per cent on guinea pig inoculations alone. Nine and three tenths per cent were found negative for tubercle bacilli by all available methods. It is interesting to note that the roentgenographic appearance of all the clinically active cases with "negative sputum" belonged to the apparently exudative and rapidly resolving type. They were diagnosed in the past as pulmonary tuberculosis because of the character and location of the lesions, though the true tuberculous nature of such cases



is often questioned nowadays. Three of them were known contact cases and their lesions were definitely incipient as proved by roentgenograms at regular intervals. Twenty of the 25 cases with stable lesions and sputum positive for tubercle bacilli were patients older than thirty-eight.

Abeles and Pinner (1) were able to demonstrate tubercle bacilli in 89.5 per cent of their series of accidentally discovered and clinically active tuberculosis by using smears, concentrations, and cultures of sputum and gastric contents. In the present study, using guinea pig inoculations, the figure for "positive sputum" in the clinically active minimal cases is 90.7 per cent. In contrast, Decker, Ordway, and Medlar (2), using all the available methods, demonstrated tubercle bacilli in only 69 per cent of their clinically active minimal cases. It appears that such a difference in the percentages of "positive" cases is due to the difference in the thoroughness and the persistence with which the search for the tubercle bacilli is made. A part of the difference may be a result of differences in the interpretation of the primary diagnostic films.

### *Blood Examination*

The Rourke and Ernstene method for determining the erythrocyte sedimentation rate has been used exclusively in this sanatorium. Any value above 0.50 mm. per minute, after correction for hematocrit, is considered elevated. In the differential study of polymorphonuclear leucocytes, if the ratio between the percentages of band and segmented forms is bigger than one to sixteen, it is considered as an evidence of "shift to the left."

In table 3 may be seen the unreliability of the blood sedimentation rate as an index of activity in minimal tuberculosis. The percentages of active and inactive cases with elevated and normal sedimentation rates are approximately the same.

Likewise, as may be seen in table 4, "shift to the left" on differential study of the polymorphonuclear leucocytes cannot be relied upon for the study of the activity of a minimal lesion.

Abeles and Pinner (1), in their study of 91 cases of accidentally discovered tuberculosis, found that the erythrocyte sedimentation rates were elevated in 62.8 per cent, and the total leucocyte counts were above normal in 43 per cent. Bobrowitz, Hurst, and Martin (3) found no apparent relation between sedimentation rates, total leucocyte counts, and incidence of progression.

### *Symptomatology*

In the present series, the most common complaints were fatigue (42.6 per cent) and cough (35.4 per cent). Hemoptysis or blood-streaking prior to admission was reported in 18.3 per cent of the cases, one-third of whom were found to be inactive. Seven of the 9 cases of hemoptysis, with inactive lesions, were older than thirty-eight. More than half of the incipient cases denied symptoms at any time. In the group of patients with no symptoms, the lesions of all the 9 patients older than thirty-eight proved to be inactive, while only 3 of the 23 patients younger than twenty-five were inactive. In the group of patients with

symptoms, the lesions of 20 of the 32 patients older than thirty-eight, and 36 of the 40 patients younger than twenty-five, were active.

Thus it appears that, in the older patients, the presence of symptoms is of lesser importance in deciding the activity of a lesion, while their absence strongly suggests inactivity. Conversely, any symptom of the younger patients should be carefully evaluated, and the absence of symptoms should never be considered as evidence of inactivity.

TABLE 3

*Percentages of normal and elevated erythrocyte sedimentation rates in active and inactive cases*

|                     | ELEVATED SEDIMENTATION<br>RATE | NORMAL SEDIMENTATION<br>RATE |
|---------------------|--------------------------------|------------------------------|
|                     | <i>per cent</i>                | <i>per cent</i>              |
| Active cases.....   | 47.1                           | 52.9                         |
| Inactive cases..... | 48.9                           | 51.1                         |

TABLE 4

*Percentages of normal and abnormal ratio between band and segmented forms of polymorphonuclear leucocytes in active and inactive cases*

|                     | ABNORMAL RATIO BETWEEN<br>BAND AND SEGMENTED FORMS | NORMAL RATIO BETWEEN<br>BAND AND SEGMENTED FORMS |
|---------------------|--|--|
|                     | <i>per cent</i>                                    | <i>per cent</i>                                  |
| Active cases.....   | 42   | 58   |
| Inactive cases..... | 22.2   | 77.8   |

TABLE 5

*Number and percentages of active cases in different age groups*

|                                  | BELOW 25 | 25 TO 38 | ABOVE 38 |
|----------------------------------|----------|----------|----------|
| Total number of patients.....    | 63       | 60       | 41       |
| Number of active cases.....      | 56       | 43       | 20       |
| Percentages of active cases..... | 88.9     | 71.7     | 48.8     |

### *Activity of Lesions*

The number of active cases found in the three age groups (table 5) reveals a much higher percentage of activity in the younger patients. Fifty-one per cent of the lesions discovered in patients older than thirty-eight were inactive. Probably the percentage of inactive cases in general surveys is even higher than these values, as the present study is concerned with a group of patients referred for observation and treatment.

### *Incidence of Progression*

In table 6 are presented the subsequent course of the active lesions found in different age groups. As expected, regardless of their character, lesions in the

younger patients have a much higher rate of progression than those in the older group. Bobrowitz, Hurst, and Martin (3) found that productive-fibrotic and fibro-calcific lesions had as high a progression rate as exudative and exudative-productive lesions in patients under twenty-five, and they concluded that the age was the most significant factor relating to the outcome of minimal lesions. This is in accordance with the experience in this study.

### *Treatment*

The average length of sanatorium residence was 482 days for patients below twenty-five, 283 days for those between twenty-six and thirty-eight, and 263 days for those above thirty-eight. The percentage of patients receiving pneumothorax treatment was 60.7 per cent in patients below twenty-five, 44.2 per cent

TABLE 6

*Number and percentages of progressive, regressive, and stable lesions in different age groups*

| LESIONS              | AGE             |          |                 |          |                 |          |
|----------------------|-----------------|----------|-----------------|----------|-----------------|----------|
|                      | Below 25        |          | 25 to 38        |          | Above 38        |          |
|                      | Number of cases | Per cent | Number of cases | Per cent | Number of cases | Per cent |
| Progressive.....     | 27              | 48.2     | 17              | 39.5     | 1               | 5        |
| Regressive.....      | 13              | 23.2     | 15              | 34.9     | 5               | 25       |
| Stable.....          | 6               | 10.7     | 5               | 11.6     | 14              | 70       |
| No observation*..... | 10              | 17.9     | 6               | 14       | 0               | —        |

\* Represents those cases in which pneumothoraces were induced immediately after sputum was found positive, without a period of observation.

in those between twenty-six and thirty-eight, and none in those above thirty-eight.

There were two deaths resulting from progressive tuberculosis in the whole series. The other 162 patients were discharged as apparently arrested or quiescent. Further hospitalization was not insisted upon for those intelligent patients with favorable socio-economic conditions when their clinical status reached the stage of quiescence. They were allowed to go home and be followed regularly outside. There were 17 reactivations among the 119 clinically active cases, with no appreciable difference between those discharged as apparently arrested or quiescent. There were no reactivations among the 45 cases considered inactive. The percentages of reactivation in different age groups show no significant difference.

### DISCUSSION

The importance of determining the potentialities of a minimal lesion is obvious. Serial roentgenograms and intensive bacteriological study are, perhaps, the only reliable criteria and both of these require a relatively long period to be of any conclusive value. During that period the question of management necessarily arises. While the sanatorium is undoubtedly the most ideal place for such ob-

servation, the socio-economic loss to the patient when kept in a sanatorium cannot be neglected. To send all the patients with minimal lesions to sanatoriums would mean unnecessary hospitalization. Conversely, to advise sanatorium treatment only when there is evidence of progress of the disease would mean losing good opportunities for arresting the disease.

Cases with definite recent infiltrates, with sputum positive for tubercle bacilli on the first few initial examinations and with definite significant symptoms, constitute only a small percentage of all minimal pulmonary tuberculosis. The status of the others remains questionable.

Of the 164 patients, 45 proved to be inactive. Twenty-five of the remaining 119 active cases had serial roentgenograms compatible with arrested tuberculosis, but were designated as active because of one or two cultures or guinea pig inoculations positive for tubercle bacilli. The significance of such findings is still disputable as far as sanatorium treatment is concerned, except in the younger patients. It may be stated again that 80 per cent of those 25 cases were in the group of patients older than thirty-eight. Thus, 42.7 per cent of the patients in the series were kept in the sanatorium for an average period of four to six months just to be told that their lesions were inactive. Had their lesions not been discovered on routine examination, they would have carried on their work and activities normally. Six months of unnecessary sanatorium residence means not only loss to the patient, but also the unnecessary occupation of sanatorium beds. In this study, the age of the patient appeared to be of great significance in the outcome of a minimal lesion. In those below twenty-five, 88.9 per cent were active and 48.2 per cent of the active cases were progressive, while in those above thirty-eight, only 48.8 per cent were active and 5 per cent of the active cases were progressive. Perhaps it is justifiable to insist on immediate hospitalization of the younger patients. For the older ones, however, especially if their socio-economic conditions are favorable and if they are willing to restrict their activities, it is better to observe them regularly at an outpatient clinic until there is definite evidence of progression.

Determining the nature and character of minimal roentgenographic lesions remains a difficult problem which cannot be solved quickly. A period of observation is always necessary. This period should be spent preferably in the sanatorium by the younger patient. It seems safe, however, to follow the older ones in the community, thus saving them considerable inconvenience and financial loss.

#### SUMMARY

A retrospective study of 164 minimal pulmonary tuberculosis cases is reported. Its significance in relation to age is emphasized.

The number of active and progressive cases is much higher in the younger than in the older patients. In the group of younger patients, treatment was more prolonged and a much higher percentage of them required collapse therapy.

Tubercle bacilli were demonstrable in 90.7 per cent of all the clinically active cases.

Study of the constituents of the blood is of little value in determining the activity of a tuberculous lesion.

Symptoms, when present, should be carefully evaluated, especially in the younger patients.

It is believed that all younger patients with minimal pulmonary lesions should be kept in sanatoriums for observation, but that older patients, if under close observation, may be followed safely in the community, thus obviating social inconvenience and financial strain.

#### SUMARIO

##### *Tuberculosis Pulmonar Mínima*

En este estudio retrospectivo de 164 casos de tuberculosis pulmonar mínima, recálcase la importancia de la edad.

El número de casos activos y progresivos es mucho mayor en los enfermos más jóvenes. En este grupo, el tratamiento fué también más prolongado y mucho mayor el porcentaje que exigió la colapsoterapia.

En 90.7 por ciento de todos los casos clínicamente activos descubriéronse bacilos tuberculosos.

El estudio de los elementos sanguíneos reviste poco valor para determinar la actividad de la lesión tuberculosa.

Los síntomas, si los hay, deben ser cuidadosamente justipreciados, máxime en los enfermos jóvenes.

Opínase que todos los enfermos jóvenes con lesiones pulmonares mínimas deben ser mantenidos en sanatorios para observación, pero que los de cierta edad, si pueden ser vigilados de cerca, pueden ser reintegrados a la colectividad, evitando así incomodidades sociales y apuros económicos.

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# PHRENIC NERVE INTERRUPTION IN THE TREATMENT OF PULMONARY TUBERCULOSIS<sup>1</sup>

A Statistical Analysis of Results in 398 Patients at Trudeau Sanatorium from  
1925 through November 1947

ROGER S. MITCHELL<sup>2</sup>

## INTRODUCTION

The question of the effectiveness of phrenic nerve interruption in the treatment of pulmonary tuberculosis has been debated for a number of years. Much enthusiasm greeted the original introduction of phrenic nerve section for pulmonary tuberculosis by Stuertz (1) in 1911. Because of frequent failures to obtain lasting and at times any hemidiaphragmatic paralysis, avulsion or exairesis was introduced independently by Felix (2) and Goetze (3) in 1922. Paralysis was then usually complete and permanent, but serious operative complications became more numerous (4-13).

The initial enthusiasm for the use of phrenic nerve interruption in extensive disease (14, 15, 16) gradually subsided. The introduction of temporary hemidiaphragmatic paralysis by phrenic nerve crush in 1927 (17), however, plus its application to less extensive disease (18), seemed to have modified the procedure sufficiently so as to make it again widely acceptable.

While this now well established type of phrenic nerve interruption has many proponents (19-25), there are others who feel that hemidiaphragmatic paralysis accomplishes little or nothing that an adequate sanatorium regimen cannot do (10, 11, 26, 27); that it is potentially dangerous (28, 29); and that it may not be an entirely sound physiological approach to the treatment of pulmonary tuberculosis (12, 30, 31).

It has been reported recently that hemidiaphragmatic paralysis, supplemented by pneumoperitoneum, may accomplish more than paralysis alone (32, 33) and that this combination is actually a form of collapse (34).

Because phrenic nerve interruption has been frequently used at Trudeau Sanatorium for over twenty years, a thorough analysis of this material should help in answering the following questions:

1. Is phrenic nerve interruption a useful form of treatment for pulmonary tuberculosis?
2. If so, in what type of case is a satisfactory result most likely to be obtained?
3. What are the early dangers and late sequelae of "temporary" phrenic nerve interruption?

An attempt to answer the first two questions is made here. The third will be considered in subsequent publications (35).

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<sup>2</sup> Associate Medical Director, Trudeau Sanatorium, Trudeau, New York.

## MATERIALS AND METHODS

Since the first phrenic nerve interruption at Trudeau Sanatorium in 1925, there have been 398 patients subjected to this procedure up to November 30, 1947. Forty-five had the permanent type (exairexis) and 353 had temporary phrenicclasis or nerve crush. Thirty-six of the latter were combined with scaleniotomy during the period from 1932 to 1936. This operation was then discontinued because its effectiveness was questioned.

Eighteen of the 398 patients had their initial phrenic nerve interruption in Saranac Lake while awaiting admission to the Sanatorium. The operation was prescribed in each case by a member of the consultant staff and carried out, two months or less prior to admission, by one of the consultant staff surgeons.<sup>3</sup> They are, therefore, included in this series.

Twenty-four patients had routine recrashes following discharge, on which complete follow-up data were obtained. These are also included as part of this study.

The clinical record of each patient was carefully reviewed, with particular attention to reports of roentgenograms and fluoroscopic studies of diaphragmatic function. The fluoroscopic studies were not routinely reported until after 1932. Consequently, evidence of hemidiaphragmatic paralysis in the early cases is unfortunately limited to observation of the position of the diaphragm on routine postero-anterior full inspiration roentgenograms.

An effort was made to review all roentgenograms available in each case in order to determine the character, location, and extent of the disease in the lung under treatment and, if present, in the opposite lung. An adequate number of roentgenograms were available in over 90 per cent of cases studied. In the balance, the roentgenogram reports in the record were utilized as far as possible. In addition, the regular yearly follow-up record of each patient was supplemented by personal letters to patients, physicians and institutions wherever indicated. Thus, as complete information as possible was obtained in 97.5 per cent of cases through late 1947.

With the accumulated data from all sources, each case was classified in each of the following ways:

1. *N.T.A. classification* before operation.
2. *Sex*.
3. *Age of patient*.
4. *Side of operation*.
5. *Relative age of the disease* in the lung under treatment, classified as:
  - (a) Recent: This classification was based on the duration and severity of symptoms, age of the patient and character of roentgen shadows, endeavoring to identify any predominantly fresh disease superimposed on old.
  - (b) Old: Similar methods were used, looking in particular for evidence of advanced pulmonary contraction, calcified nodules and secondary emphysema. The known duration of symptoms, the elapsed time since the original diagnosis and the patient's age were also considered.
  - (c) Medium: Duration of disease which fell somewhere between recent and old.
6. *Dynamic status of the disease* to be treated, during the preoperative phase:
  - (a) Improving: significant clearing and/or contraction of shadows and/or cavity by roentgenogram;
  - (b) Worse: significant increase in the area of lung involvement as seen in the roentgenogram;

<sup>3</sup> Dr. Edward S. Welles, Dr. Warriner Woodruff and Dr. Winfield O. Kelley.

(c) Same: no significant change in serial roentgenograms. The reappearance of a recently filled-in cavity, the slight enlargement of a cavity without increase in the area of disease, and very slight increases in infiltration were not classified as "worse" for the purposes of this study.

7. *Cavity walls:* These were rated as thick (roughly over 4 mm.), medium (approximately 3 to 4 mm.) and thin (1 to 2 mm.).

8. *Total average diameter of cavity or cavities* in centimeters by roentgenogram.

9. *Location of cavity or disease under treatment:* The lung was roughly divided into four gross parts:

(a) Apical (to the first interspace anteriorly).

(b) Infraclavicular.

(c) Mid-lung (including apex of lower lobe).

(d) Base.

10. *Character* or intensity of the roentgen shadows of the disease, exclusive of cavity and its wall:

(a) Heavy: very heavy mottled or uniform (pneumonic) densities.

(b) Light: very light scattered infiltration.

(c) Medium: midway between heavy and light.

11. Presence or absence of visible *fluid level within a cavity*.

12. *Endobronchial disease* as demonstrated by bronchoscopic visualization.

13. *Disease in the contralateral lung:*

(a) Cavity present.

(b) Roentgenologically active without cavity: fluffy or hazy densities and rapid change.

(c) Inactive, extensive to limited: predominantly string-like shadows, retraction, absence of cavity, and stability on serial films.

(d) Almost none or none.

14. *Maximum hemidiaphragmatic "rise,"* or failure to descend, as measured on the routine, erect, full inspiration postero-anterior roentgenogram, and classified as follows:

(a) Virtually none.

(b) Less than 1 posterior interspace.

(c) One to 2 posterior interspaces.

(d) More than 2 posterior interspaces.

15. *Total duration of paralysis,* including repeated phrenicclases, where known.

16. *Operative indications:*

(a) Cavity.

(b) Progression of disease.

(c) Positive sputum.

Other indications occurred too seldom to permit any evaluation of the effects of phrenic nerve interruption on them.

All patients were given the usual sanatorium regimen at varying levels of activity, depending on individual circumstances. In 369 (93 per cent) of the 398 patients in this series, diaphragmatic paralysis was the only collapse measure at the outset. In only 26 (7 per cent) was diaphragmatic paralysis supplementary to a homolateral pneumothorax, and in 3 (0.8 per cent) there was a coincident contralateral pneumothorax. There were none with simultaneous bilateral pneumothorax. Twenty-two had had homolateral pneumothorax previously and in 94 (24 per cent) prior attempts at homolateral pneumothorax had failed.

Results were divided into *initial* and *final*. A case was classified as an *initial good result* when all of the following conditions prevailed: (f) disappearance of cavity or



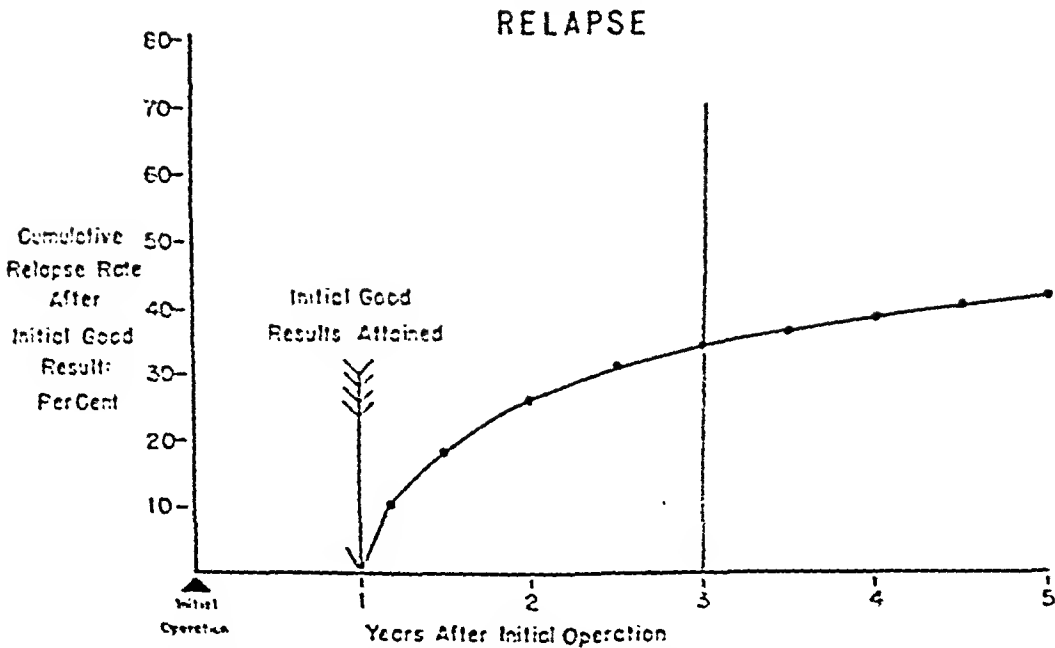


FIG. 1. Cumulative relapse rates in 107 initial good results followed five years or more.

TABLE 1

*Phrenic nerve interruptions at Trudeau Sanatorium from 1925 through November, 1947*

|                        | NUMBER OF PATIENTS | NUMBER OF "CASES"   | NUMBER OF OPERATIONS |
|------------------------|--------------------|---|----------------------|
| Phrenic exsireses..... | 45                 | 45  | 45                   |
| Phreniclasies.....     | 353                | Cases with 1 phreniclasie 251<br>Cases with 2 phreniclasies 95<br>Cases with 3 phreniclasies 14<br>Cases with 4 phreniclasies 1<br><div style="text-align: right;">361*</div> | 487                  |
| Total operations.....  | 398                | 406*  | 532                  |

\* There were 8 more "cases" than patients. They were derived as follows:

5 patients who had a second phreniclasie, on the contralateral side, one to five years after phreniclasie on the initial side.

3 patients who had a second homolateral phreniclasie for a relapse two, three and five years, respectively, after the first phreniclasie.

cavities; (2) clearing and/or contraction of infiltration; (3) absence of spread to the contralateral lung; and (4) conversion of sputum from positive for tubercle bacilli to negative<sup>4</sup> during the first twelve months following the initial operation.

<sup>4</sup> Ninety-four per cent of cases were sputum "positive" before operation. All sputum examinations were three-day concentrated smears except a few three-day concentrated cultures and gastric cultures before operation.

If such a result had not been obtained, or if pneumothorax or thoracoplasty had been deemed necessary within the first year, the case was classified as an *initial poor result*. If pneumothorax or thoracoplasty had been applied within the first four months, however, the case was excluded from the study as nonevaluable.

TABLE 2

*The reasons for the nonevaluation of 83 and exclusion of 31 of the 406 cases of phrenic nerve interruption (PNI) at Trudeau Sanatorium between 1925 and November, 1947, before making the statistical analysis*

|  | PHRENIC<br>EXAIRESIS | PHRENICLASIS | TOTAL |
|--|----------------------|--------------|-------|
| Total number of cases.....   | 45                   | 361          | 406   |
| Total evaluated cases studied statistically.....   | 39                   | 253          | 292   |
| <i>Total cases excluded from study:</i> .....  | 6                    | 108          | 114   |
| No paralysis obtained.....   | 2                    | 14           | 16    |
| Questionable or insufficient paralysis.....  | 1                    | 3            | 4     |
| Phrenic nerve interruption not completed.....  | 0                    | 1            | 1     |
| Cavity closure occurred over one year after hemidiaphragmatic paralysis.....   | 2                    | 2            | 4     |
| Pneumothorax added one month later.....  | 0                    | 1            | 1     |
| Pneumothorax probably responsible for cavity closure.....  | 0                    | 1            | 1     |
| Cavity closed but developed severe contralateral spread.....   | 0                    | 1            | 1     |
| Relapse roughly coincident with return of hemidiaphragmatic function.....  | —                    | 12           | 12    |
| Insufficient evidence of active disease requiring collapse in retrospect.....  | 0                    | 5            | 5     |
| Operation performed to assist in obliteration of old pneumothorax space.....   | 1                    | 0            | 1     |
| No or insufficient follow-up data:   |                      |              |       |
| (a) First PNI performed prior to January 1, 1945.....  | 0                    | 6            | 6     |
| (b) First PNI performed after January 1, 1945 and <i>initial good</i> results obtained.....  | —                    | 31           | 31    |
| (Evaluated, but first PNI performed after January 1, 1945 with <i>initial poor</i> results; excluded to balance the above <i>initial good</i> results without three-year follow-up)..... | —                    | 31           | 31    |
|  | 6                    | 108          | 114   |

A *final good result* was arbitrarily defined as an initial good result following which the patient remained well and working without relapse for two more years, or for three years after initial hemidiaphragmatic paralysis. There were 107 patients with initial good results who were followed for at least five years. Figure 1 shows the cumulative relapse rate in this group for each six-month period for five years. The 45 relapses were homo-

lateral in 31, contralateral in 2, bilateral in 7, and location not known in 5. The incidence of relapse is seen to have completely leveled off at around three years, at which time 84 per cent of the relapses had already occurred. In a rough fashion, therefore, the rather high incidence of relapse occurring through the second and third years is attributed to failure of treatment, while the occasional relapse occurring through the succeeding eighteen years is simply an indication of the chronic relapsing nature of the disease.

All second- and third-year relapses after an initial good result, and also all initial poor results, were classified as *final poor results*.

In table 1 are presented the number of patients, cases and operations. Although there were 398 patients in the series, there were 406 "cases" to be evaluated. There were 8 more cases than patients because 5 patients had contralateral phreniclasia one to five years after their initial phreniclasia, and 3 patients had a repeat homolateral phreniclasia for a relapse occurring two, three and five years, respectively, after return of function of the hemidiaphragm following the first phreniclasia.

Table 2 outlines the reasons for the exclusion from statistical analysis of 114 of the 406 cases. In the first place, the 62 cases in which initial phrenic nerve interruption was performed after January 1, 1945, were excluded. The reason for the exclusion was, first, that 31 cases with initial good results had not had a three year follow-up. In addition, the other 31 cases after January 1, 1945, had initial poor results and were, therefore, also excluded in order to prevent weighting the entire series. It is worth noting that about the same proportion of initial good results (i.e. 50 per cent) holds in these 62 excluded cases as in the 292 evaluated cases.

Relapse roughly coincident with return of hemidiaphragmatic function was observed in 12 cases. These cases were not classified as poor, as it was felt that the procedure had not been given a fair trial because of failure to repeat phreniclasia. It is of additional interest that 14 other cases, which were improving but insufficiently to be classified as initial good results, also showed distinct progression of disease coincident with return of hemidiaphragmatic function.

## RESULTS

All results are based upon an analysis of the previously defined, fully evaluated series of 292 cases.

As may be seen in figure 2, approximately one-third of the exaireses were initially successful and one-fifth maintained their gain, while about one-half of the temporary phrenic nerve interruptions showed initial good results with about one-third attaining final good results. It will be seen that the difference in height between the crosshatched portion of the left- and right-hand columns in these figures gives a graphic representation of the relapse rate. Table 3 is an analysis of *initial* and *final* results expressed in both number of cases and percent.<sup>5</sup>

In figure 1, it will be seen that the cumulative relapse rate following initial good results in the series of 107 cases followed five years or more was as shown in table 4.

Figure 3 shows graphically the total number of initial phrenic nerve interruptions performed per year and curves of the relative effectiveness attained, as

<sup>5</sup> The statistics presented were prepared with the assistance of Mr. Malcolm S. McComb, economist with the Federal Government, and a number of volunteer rehabilitating sanatorium patients, to whom the author is indebted.

# TYPE OF OPERATION

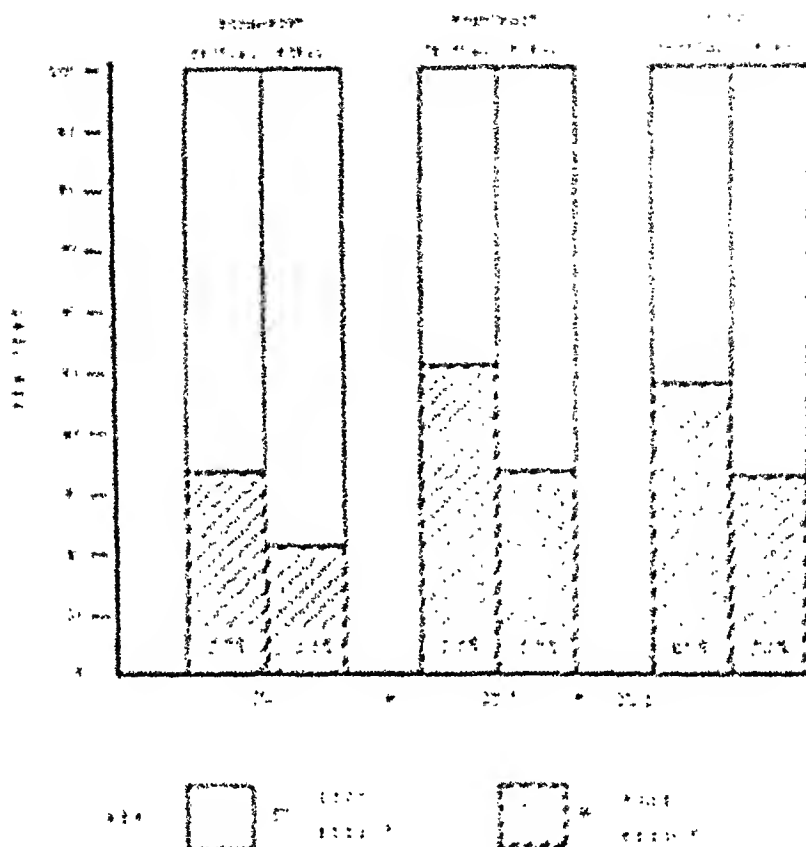


Fig. 1. Distribution of type of operation in the group of patients with a diagnosis of cancer of the breast.

## RESULTS

Analysis of the results of the study shows that the most common type of operation performed in the group of patients with a diagnosis of cancer of the breast was the mastectomy.

| Operation  | Mastectomy |    | Mastectomy with axillary lymph node dissection |    | Mastectomy with axillary lymph node dissection and contralateral mastectomy |   |
|--|------------|----|--|----|---|---|
|  | Number     | %  | Number   | %  | Number  | % |
| Total  |            |    |  |    |   |   |
| Mastectomy   | 10         | 22 | 10   | 22 | 1   | 2 |
| Mastectomy with axillary lymph node dissection   | 2          | 4  | 10   | 22 | 1   | 2 |
| Total  |            |    |  |    |   |   |
| Mastectomy with axillary lymph node dissection   | 2          | 4  | 10   | 22 | 1   | 2 |
| Mastectomy with axillary lymph node dissection and contralateral mastectomy                                    | 1          | 2  | 1  | 2  | 1   | 2 |
| Total  |            |    |  |    |   |   |
| Mastectomy with axillary lymph node dissection   | 1          | 2  | 1  | 2  | 1   | 2 |
| Mastectomy with axillary lymph node dissection and contralateral mastectomy                                    | 1          | 2  | 1  | 2  | 1   | 2 |
| Mastectomy with axillary lymph node dissection and contralateral mastectomy and axillary lymph node dissection | 1          | 2  | 1  | 2  | 1   | 2 |
| Total  |            |    |  |    |   |   |
| Mastectomy with axillary lymph node dissection   | 1          | 2  | 1  | 2  | 1   | 2 |
| Mastectomy with axillary lymph node dissection and contralateral mastectomy                                    | 1          | 2  | 1  | 2  | 1   | 2 |
| Mastectomy with axillary lymph node dissection and contralateral mastectomy and axillary lymph node dissection | 1          | 2  | 1  | 2  | 1   | 2 |

measured by initial and final results in the evaluated series. Use of the procedure gradually increased to 1944; since then it has declined. Maximum effectiveness is shown in 1943-44, the last period reported, as evidenced by final good results of 43 per cent.

TABLE 4  
*Cumulative relapse rate after initially successful phrenic nerve interruption*

| YEARS AFTER INITIAL OPERATION | PER CENT |
|-------------------------------|----------|
| years                         |          |
| 1½                            | 18       |
| 2                             | 25       |
| 3                             | 34       |
| 4                             | 37       |
| 5                             | 40       |

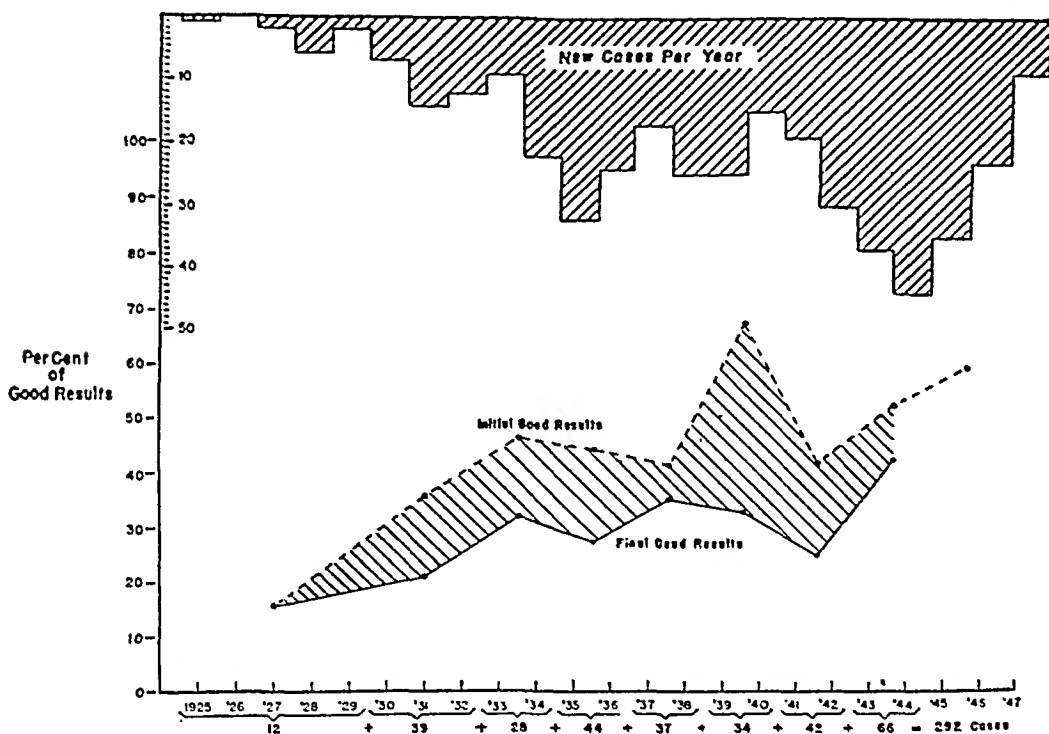


FIG. 3. The frequency of use and relative effectiveness of phrenic nerve interruption at Trudeau Sanatorium between 1925 and 1947.

The age range was 15 to 56 years, with 31 per cent, 15 to 25; 59 per cent, 26 to 40; and 10 per cent, 41 to 56. Final results were quite similar in the two sexes and in the three age groups<sup>6</sup>. Age range and distribution of the entire series of 406 cases was entirely comparable to the 292 cases reported.

<sup>6</sup> Figure 4, *Relation of results to age and sex*, was omitted because of limitations of space.

The extent of disease, as measured by the standard National Tuberculosis Association classification, at the time of initial operation is shown in figure 5 to have influenced results materially. The heavily preponderant group of moderately advanced cases responded much more favorably than the far advanced group. There were only 2 minimal cases, each with a good result.

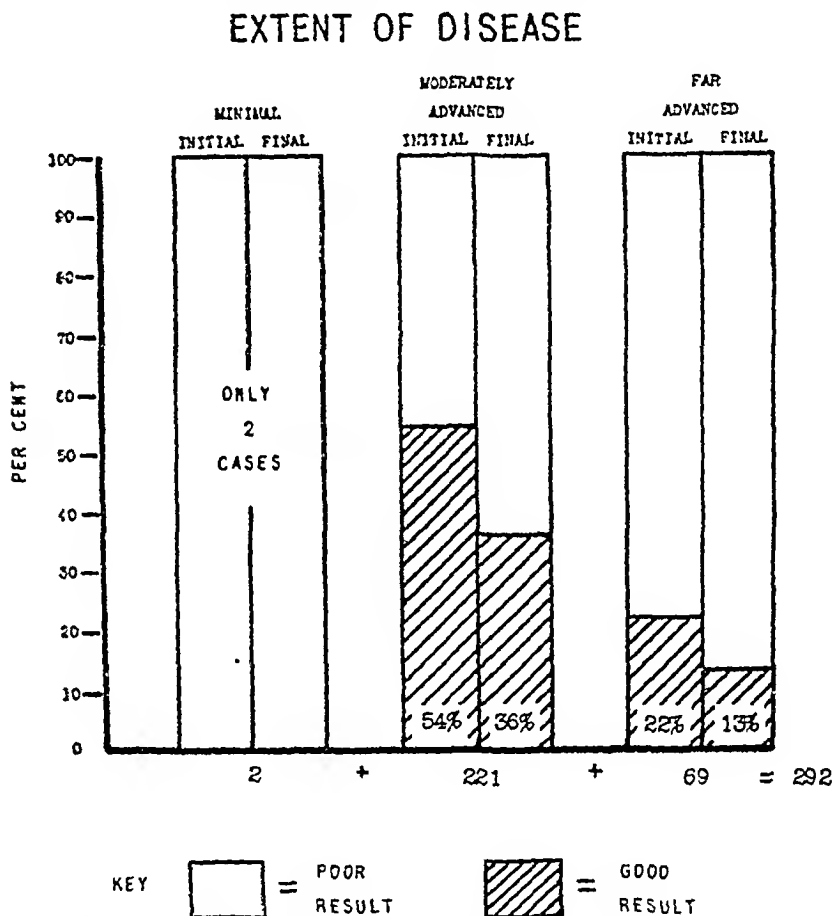


FIG. 5. Relation of extent of disease to results with phrenic nerve interruption.

Results on the right and left sides were almost identical, both with regard to initial success and tendency to relapse.

Figure 6 indicates that disease which was showing distinct improvement under observation responded much better than relatively static disease, and still better than disease which was getting distinctly worse before operation.

Figure 7 indicates clearly that both initial and final results were quite poor with old well-established disease as compared to diseases of medium age or of relatively recent origin.

Figure 8 shows that results were essentially independent of the location of the disease in the lung. Mid-lung and basal lesions showed the best initial results,

but a very high relapse rate made final results with basal lesions the poorest of all. Results in infraclavicular and mid-lung lesions were slightly better than in apical. Six of 12 patients with cavities in two different locations had initial good results and none relapsed.

Figure 9 reveals the striking improvement in results as the procedure was applied to smaller (less than 2 cm.) cavities.

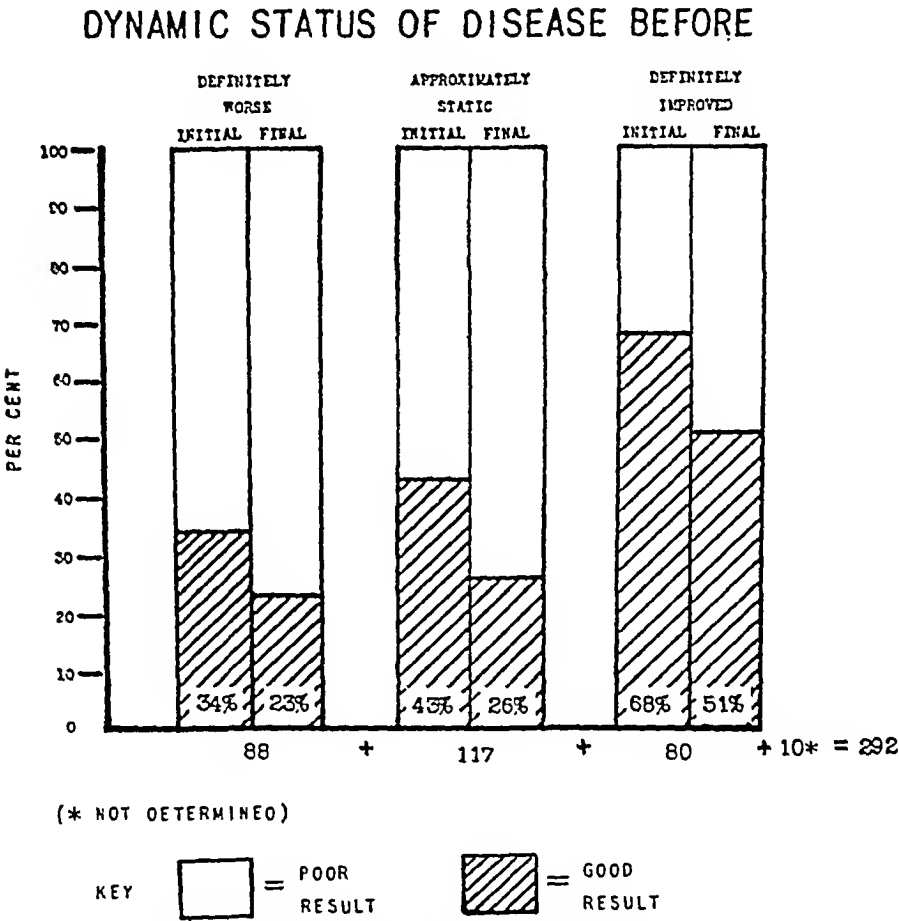


FIG. 6. Relation of dynamic status of disease before operation to results with phrenic nerve interruption.

Figure 10 indicates that thin-walled cavities responded better than medium- and thick-walled cavities, but that there were 24 per cent final good results with the thick-walled variety.

Out of a total of 208 cases with cavity, fluid level was found in 7. Three of these showed an initial good result and 2 a final good result after phrenic nerve interruption.

Forty-three patients in this series were subjected to bronchoscopy shortly before or after initial operation. The results in this group may be seen in table 5.

The character or intensity of the roentgen shadows, exclusive of cavity wall, is shown by figure 11 to have influenced results. In general, the denser the shadows, the worse were the results.

The preoperative extent and activity of disease in the contralateral lung (figure 12) was also found to have been closely related to results. Any cavity in the contralateral lung was very apt to be associated with homolateral failure, while final

### ESTIMATED AGE OF DISEASE

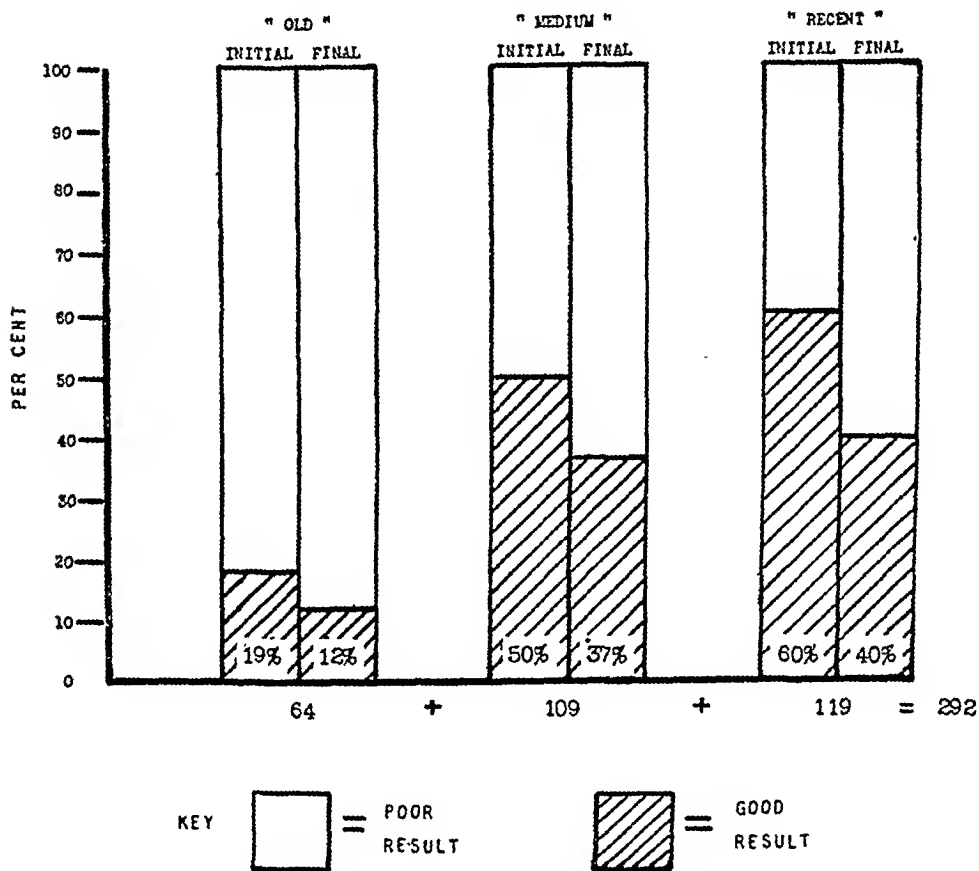


FIG. 7. Relation of estimated age of disease under treatment to results with phrenic nerve interruption.

good results were apparently unaffected by the extent or activity of disease in the contralateral lung in the absence of cavity.

The fate of the disease in the contralateral lung within three months after phrenic nerve interruption is shown in figure 13. It is clear that cavitary disease was very apt to deteriorate; that roentgenologically active noncavitary disease and also very small foci of disease were rather apt to deteriorate; that well arrested old disease was not apt to be affected in spite of its extent; and, finally, that when no disease was present at the time of operation, spread was not seen.



A less profound relationship of the preoperative condition of the contralateral lung to results has been previously reported (22).

There were 31 of the 292 evaluated cases which did not have cavity at the time of phrenic nerve interruption. Four operations given to help obliterate an empyema space and one to stop hemorrhage were classified as initial poor results. In 12 cases where the indication for operation was sputum persistently positive for tubercle bacilli, and in 14 cases with progression of disease, the incidence of

### LOCATION OF CAVITY OR DISEASE

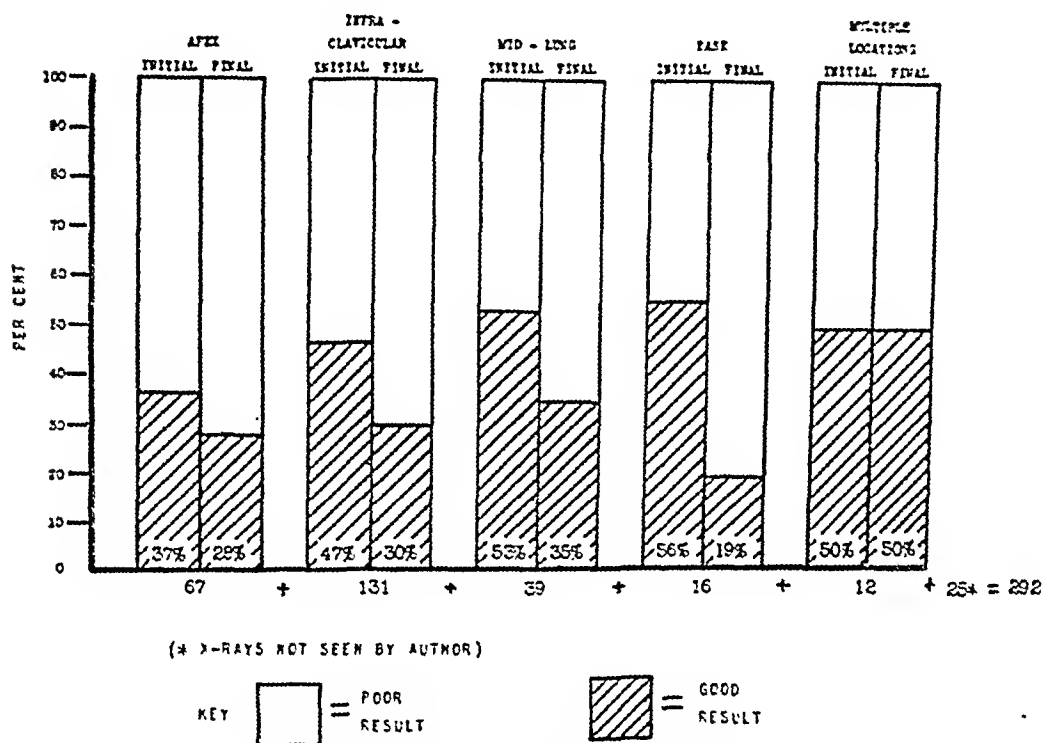


FIG. 8. Relation of location of cavity or disease under treatment to results with phrenic nerve interruption.

initial and final good results was approximately the same as for the group as a whole.

Final results in 33 cases, wherein a cavity became replaced by a localized area of cloudiness ("filled-in") after phrenic nerve interruption, were good in 36 per cent, poor in 55 per cent and undetermined in 9 per cent.

Figure 14 indicates a positive relationship between results and the position of the hemidiaphragm on full inspiration, so-called "rise." When the hemidiaphragm showed maximal elevation (e.g., two posterior interspaces or more above its preoperative level on full inspiration), initial good results in a series of 38 patients were higher (66 per cent) than for any other factor studied; more important, the relapse rate was negligible.

There were 22 cases with clear-cut fluoroscopic evidence of preoperative limitation of a hemidiaphragm which was later successfully paralyzed. In 19 of these, the writer was able to compare the postoperative level of the hemidiaphragm with its preoperative level. Twelve showed a rise of less than one posterior interspace; there were 6 with a rise of between one and two, and 1 with a rise of over two posterior interspaces. In addition, there were 41 per cent initial and

### SIZE OF CAVITY

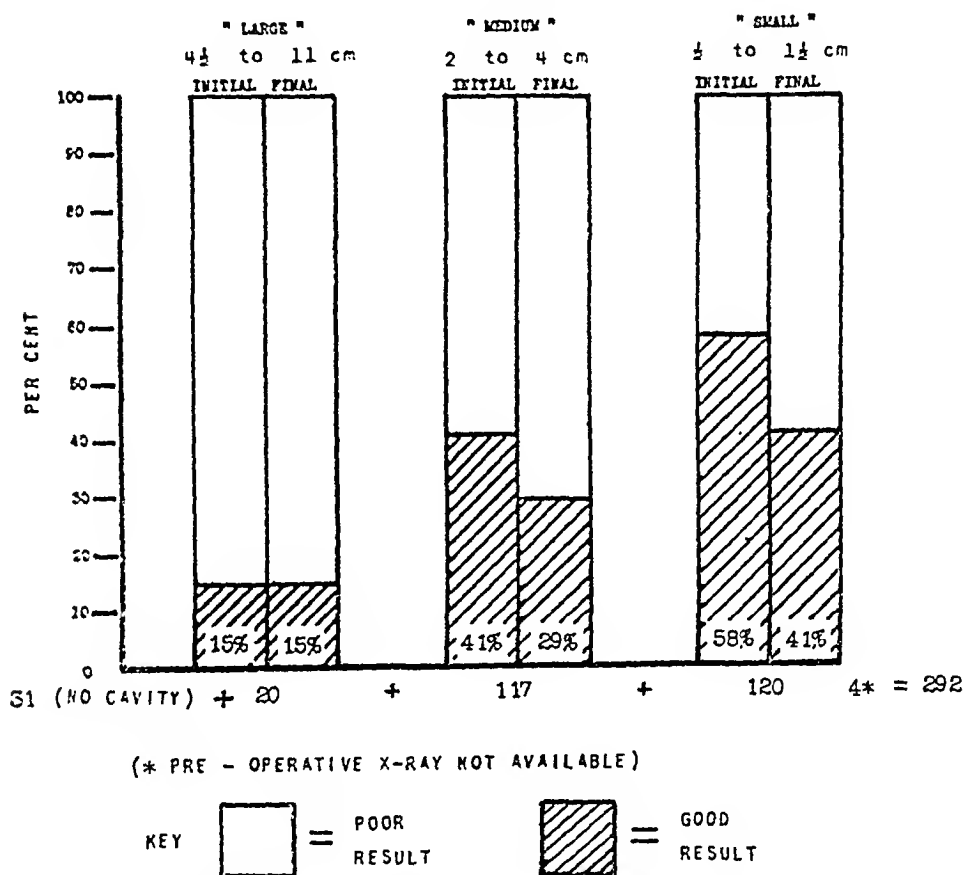


FIG. 9. Relation of size of cavity to results with phrenic nerve interruption.

32 per cent final good results in the 22 cases showing relative preoperative hemidiaphragmatic limitation.

In order to assess the effect of relative obliteration of the intrapleural space on results with phrenic nerve interruption, the cases were divided into four groups, as may be seen in table 6. The group in which pneumothorax had not been attempted is weighted in the direction of less disease because of a policy in general of prescribing pneumothorax, rather than phrenic nerve interruption, for more extensive disease.

The approximate total duration of paralysis from all operations was determined

## CAVITY WALL

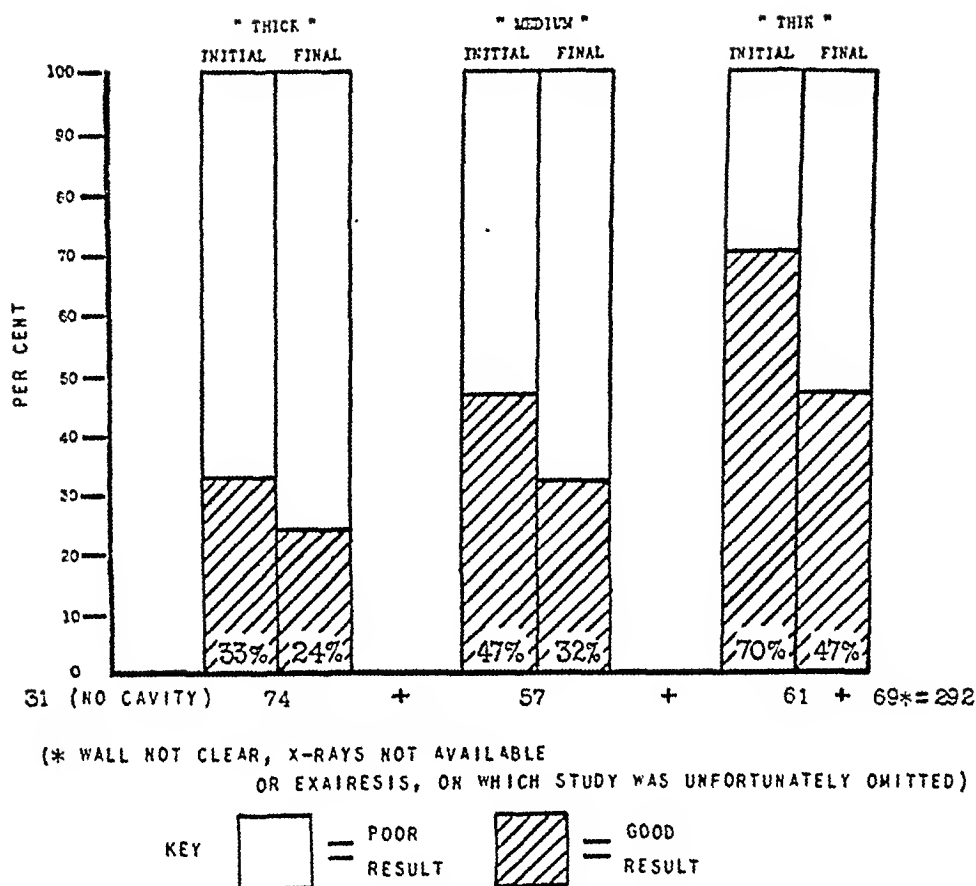


FIG. 10. Relation of thickness of cavity wall to results with phrenic nerve interruption.

TABLE 5

*Cumulative relation of endobronchial tuberculosis to results with phrenic nerve interruption*

| VISIBLE ENDOBRONCHIAL TUBERCULOSIS | NUMBER OF CASES | GOOD RESULTS |          |
|------------------------------------|-----------------|--------------|----------|
|                                    |                 | Initial      | Final    |
|                                    |                 | per cent     | per cent |
| Homolateral.....                   | 19              | 32           | 10       |
| None seen.....                     | 23              | 21           | 21       |
| Total.....                         | 43*             |              |          |

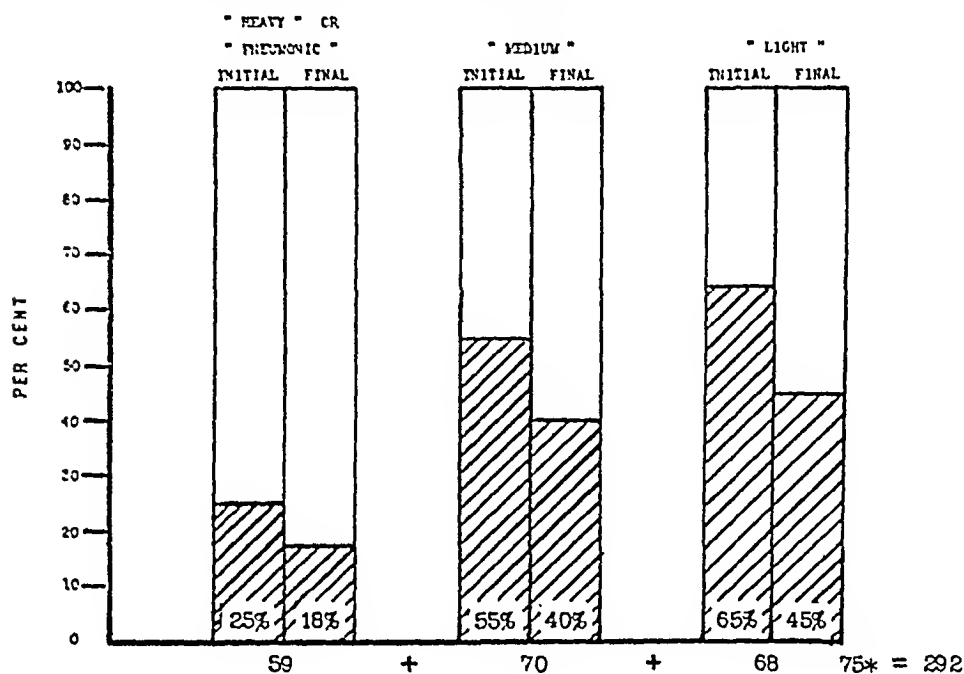
\* Includes one case with contralateral endobronchial disease, in which a poor result was observed.

in 125 of the 253 cases of temporary phrenic nerve interruption included in the study. Three unintentional permanent paralyses were arbitrarily given the value of thirty-six months. In table 7 may be seen calculations of both the mean

and median total duration of paralysis for the subgroups: initial poor result; initial good result with relapse within three years; and final good result.

The use of supplementary scaleniotomy in 33 cases yielded good results initially in 42 per cent and finally in 27 per cent. These figures were poorer than for the group as a whole but it should be noted that the operation was in use only from 1932 to 1936.

## CHARACTER OF ROENTGEN SHADOWS



(\* CLASSIFICATION NOT CLEAR OR X-RAYS NOT SEEN BY AUTHOR)



FIG. 11. Relation of character of the roentgen shadows exclusive of cavity wall, if present, to results with phrenic nerve interruption.

The 94 good results were studied more closely to measure, insofar as possible, how much phrenic nerve interruption had contributed to bed-rest, or vice versa, in the arrest of the disease. All patients who had progressed to the point where they were up and about for six or more hours per day were considered to have been graduated from a bed-rest status. Using this arbitrary definition and including time in bed before admission to the Sanatorium, table 8 shows the consecutive preoperative bed-rest in the series of 292 cases. Only 17 of the patients with final good results spent six months or more of this bed-rest at Trudeau

Sanatorium, and only 9 spent the major part of the six months at as strict a level as twenty-two to twenty-three hours a day in bed in an infirmary.

In assessing definite accomplishments in the 94 final good results, 41 were found to have been improving before operation, 33 were approximately unchanged, and only 20 were getting worse during the preoperative period. Review of these 20 cases, worse before operation, revealed that 5 of them were noncavitary and that 9 had cavities of 1 cm. or less in diameter.

### DISEASE IN CONTRALATERAL LUNG

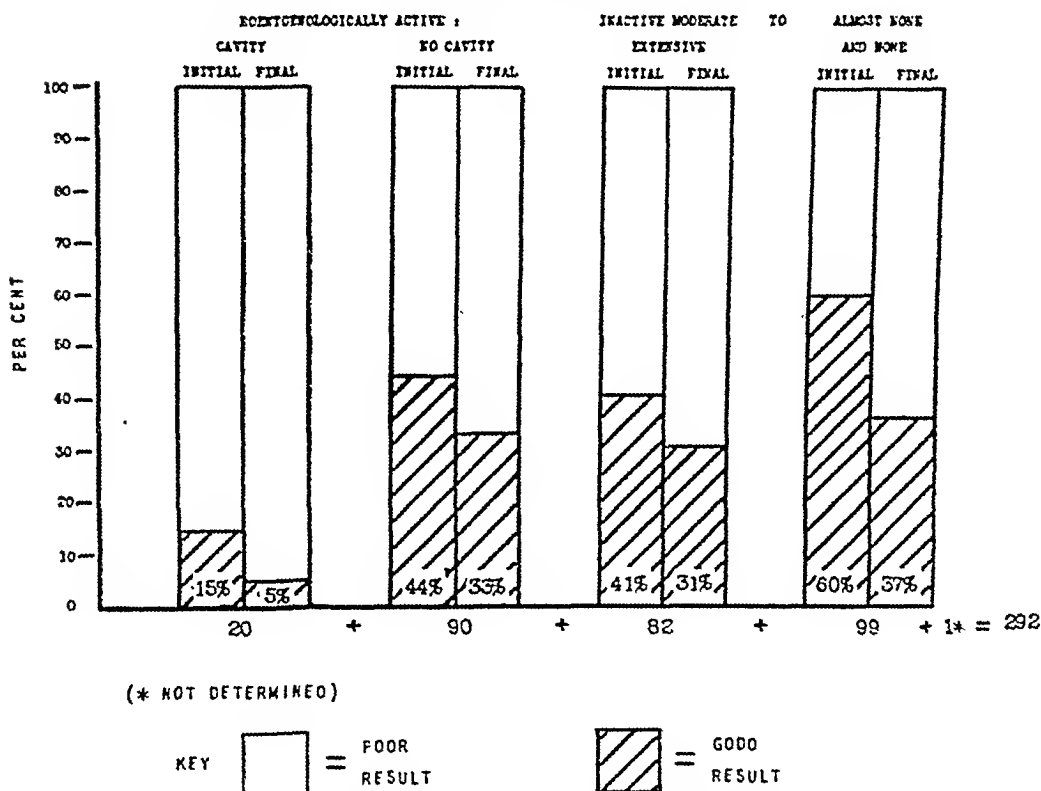


FIG. 12. Relation of extent and activity of disease in contralateral lung to results with phrenic nerve interruption.

The duration of postoperative sanatorium residence may be seen in table 9. As indicated in the table, patients with later relapse were given as much postoperative sanatorium treatment as the group which remained well.

In the course of reviewing preoperative roentgenograms and clinical data, the author divided all cases according to modern criteria into the two groups, acceptable and nonacceptable risks for success with phrenic nerve interruption. The criteria used were based upon a consensus of the current opinion of the consultant staff of Trudeau Sanatorium and were as follows: (1) a limited amount of not too old or destructive disease, preferably not getting worse before operation; (2)

cavity not over 3 cm. in diameter, and preferably smaller; (3) in more advanced disease, only after pneumothorax failure or when thoracoplasty is contraindicated or refused (a criterion not used in determining acceptability of cases in this study); (4) no respiratory distress; and (5) no obstructive endobronchial tuberculosis.

## FATE OF DISEASE IN CONTRALATERAL LUNG

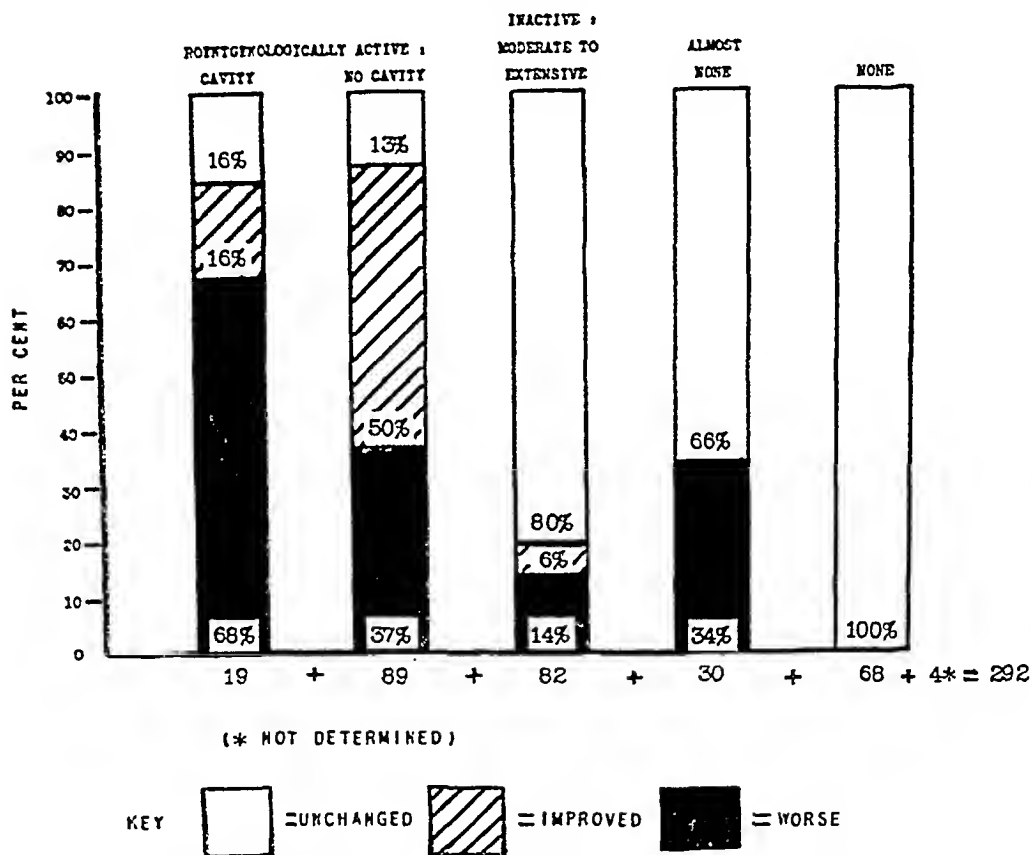
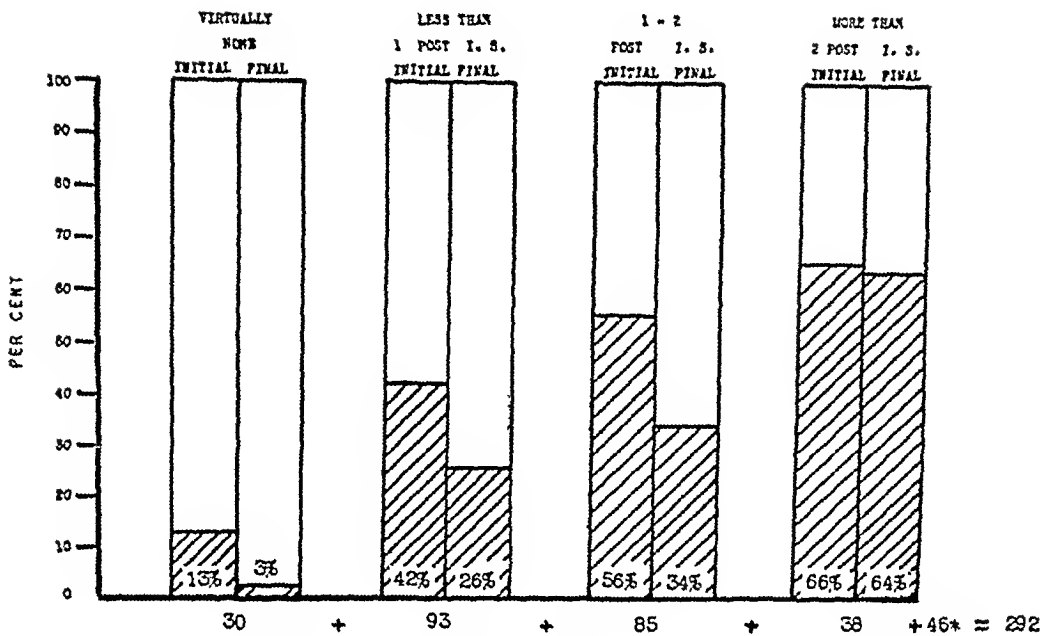


FIG. 13. The fate of disease in the contralateral lung soon after phrenic nerve interruption.

In the writer's selection, many of the exigencies of the individual personal situations obviously were not considered. Cases were selected for likelihood of success on the basis of these rather rigid roentgen and clinical criteria only.

Figure 15 shows the results obtained in these two series. Attention is first called to the fact that, while the results in the acceptable group were considerably better than in the group as a whole (figure 2), 15 per cent (16 cases) of unpredictable good results occurred in the nonacceptable group. Eleven of these 16 unexpected good results were all the more striking when it was found that they had

## "RISE" OF HEMIDIAPHRAGM



(\* INADEQUATE FLUOROSCOPY REPORTS AND/OR X-RAYS AVAILABLE TO AUTHOR)

KEY  = POOR RESULT  = GOOD RESULT

FIG. 14. Relation of hemidiaphragmatic "rise" to results with phrenic nerve interruption.

TABLE 6

*Relation of condition of pleural space to results with phrenic nerve interruption*

| CONDITION OF PLEURA AS EVIDENCED BY<br>PREOPERATIVE HOMOLATERAL PNEUMOTHORAX | NUMBER OF CASES | GOOD RESULTS        |                   |
|--|-----------------|---------------------|-------------------|
|  |                 | Initial<br>per cent | Final<br>per cent |
| Previous pneumothorax treatment,<br>later abandoned.....                     | 19              | 16                  | 5                 |
| Concurrent pneumothorax treatment..  | 20              | 35                  | 20                |
| No pneumothorax space found after<br>repeated attempts.....                  | 84              | 37                  | 21                |
| Pneumothorax not attempted.....  | 169             | 60                  | 42                |
| Total cases.....   | 292             |                     |                   |

failed to improve on six months or more bed-rest just before operation. In addition, there were 37 per cent (66 cases) of initial poor results in the acceptable group. A careful review of the clinical data and roentgenograms of these un-

accountable results was made in an effort to identify, if possible, some common denominator which might make them more predictable in retrospect. By "unaccountably good" is meant the presence of at least several attributes such as

TABLE 7

*Relation of duration of paralysis to results with phrenic nerve interruption*

| RESULTS  | NUMBER OF CASES | DURATION OF PARALYSIS |                     |
|--|-----------------|-----------------------|---------------------|
|  |                 | Mean                  | Median              |
| Initial poor result.....                                     | 31              | <i>month</i><br>10.3  | <i>month</i><br>8.5 |
| Initial good results with relapse within<br>three years..... | 28              | 10.4                  | 8.5                 |
| Final good result.....                                       | 66              | 14.3                  | 12.0                |
| Total.....   | 125             |                       |                     |

TABLE 8

*Relation of consecutive bed-rest immediately before operation to results with phrenic nerve interruption*

| CONSECUTIVE BED-REST BOTH BEFORE<br>ADMISSION AND IN THE SANATORIUM | NUMBER OF CASES | GOOD RESULTS |          |        |          |
|---|-----------------|--------------|----------|--------|----------|
|   |                 | Initial      |          | Final  |          |
|   |                 | Number       | Per cent | Number | Per cent |
| Less than 2 months.....   | 64              | 40           | 62       | 29     | 45       |
| 2 to 4 months.....  | 64              | 35           | 55       | 20     | 31       |
| 4 to 6 months.....  | 57              | 27           | 47       | 18     | 32       |
| over 6 months.....  | 107             | 39           | 36       | 27     | 25       |
| Totals.....   | 292             | 141          |          | 94     |          |

TABLE 9

*Relation of results with phrenic nerve interruption to duration of postoperative sanatorium residence*

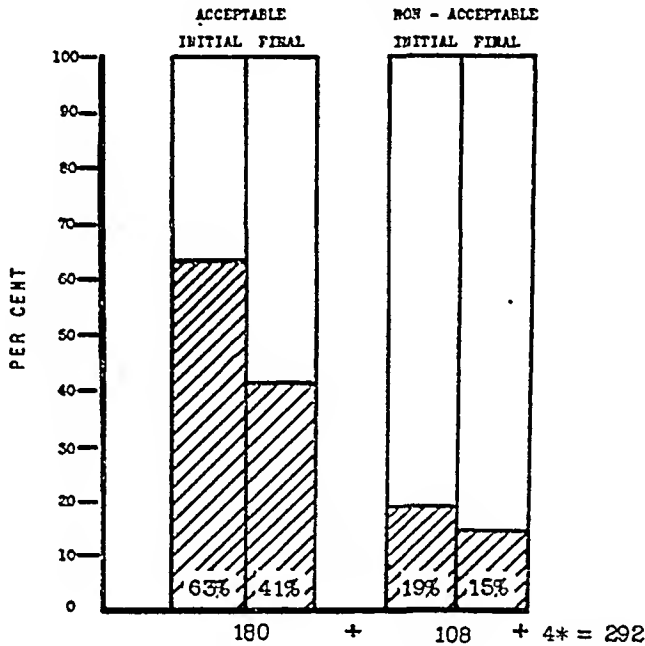
| RESULTS  | NUMBER OF CASES | DURATION OF POSTOPERATIVE SANATORIUM<br>RESIDENCE IN MONTHS |        |
|--|-----------------|---|--------|
|  |                 | Mean  | Median |
| Initial good results with relapse<br>within three years..... | 47              | 9.4   | 12     |
| Final good results.....                                      | 94              | 10  | 10     |

large cavity, apparently old or progressive disease, extensive disease in the contralateral lung, and the like, which should have led to a poor result. By "unaccountably poor" is meant a case with no attribute which should have prevented a good result according to current standards.



There seemed to be one factor present in most of these unaccountably good results which was usually not evident in the unaccountably poor results. This was the finding, on serial preoperative roentgenograms, of a progressive tendency of the diseased lung to contract, as evidenced by one or more of the following: (1) strand-like shadows radiating from the lung root; (2) slight retraction of the

EFFECT OF "SELECTION" ON RESULTS



(\* ACCEPTABILITY NOT DETERMINED)



KEY       = POOR RESULT       = GOOD RESULT

FIG. 15. Results with phrenic nerve interruption at Trudeau Sanatorium: results in two groups, one determined acceptable, and the other nonacceptable, by author, according to modern criteria.

trachea, heart, or great vessels; (3) upward displacement of the hilum; and (4) upward displacement of the hemidiaphragm.

COMMENT

The statistical accuracy of a study of the results of any treatment of pulmonary tuberculosis is affected by various unmeasurable factors, such as changes in the immunological response, emotional problems, the individual degree of adherence to the prescribed sanatorium regimen, state of nutrition, dietary habits, supplementary forms of treatment, and the convictions of the writer.

An interesting check on the clinical observations forming the basis for the present study is provided by an independent survey of the first 177 of the same patients by Yeager (36) in 1942. Using entirely different methods and criteria, he nevertheless found 55 per cent "initial" and 37 per cent "final" good results, values which check rather closely with the results reported herein.

It is well recognized that the arbitrary criteria for results chosen for this study are open to criticism. On the one hand, proponents of phrenic nerve interruption may well ask whether one can dismiss the partial benefits of the operation in the group which failed to achieve control of disease within one year. It may also be questioned whether spread of disease to the contralateral lung, coincident with homolateral control of disease, is a failure of a unilateral measure. (There were four such instances classified as poor results in the series.) Failure to "convert" a sputum positive for tubercle bacilli with a unilateral procedure in bilaterally active disease may also be questioned. (There was one such instance in this series.) Finally, it is questionable whether a purely contralateral relapse is evidence of final failure of a unilateral procedure. (There were three such instances in this series.)

Cavity closure and sputum "conversion" were not analyzed separately since one without the other has much less significance than the combination, and sputum "conversion" alone depends upon too many uncontrollable variables.

Contrariwise, it may be argued that all relapses occurring through five years, or even more, after operation should be considered as failures. Moreover, it may be maintained that much of the apparent benefit of hemidiaphragmatic paralysis may be attributed to bed-rest and the sanatorium regimen, as the demonstrable physiological effects are limited in comparison with other collapse measures (31, 37).

In figure 3 it is of interest to note that an unusual peak of initial good results, 65 per cent in 1942, was reduced by relapses to the average final good result level of 33 per cent. In addition, the percentage of final good results in patients receiving initial phrenicectomy in 1943-1944 was high. The follow-up information for the third year of many of these patients was determined from reports dated in late 1947. From experience gained in the discovery and dating of relapses, it is felt that follow-up through an additional few months, including sputum and roentgen studies, might well have led to the clinical discovery of relapses which had their unsuspected symptomatic onset sometime within the third postoperative year.

The data in figure 3 further reveal that the results have shown a tendency to improve as years have passed. This may be explained in part by the fact that the first phrenicectomy in the series was in 1932, while the last exeresis was in 1934. Most authors have reported the more dependable results after phrenicectomy. More important, probably, is the factor of improvement in selection of cases by experience.

It is well to emphasize that no information on the effect of phrenic nerve interruption in either minimal or incipient tuberculosis was obtained from this study. In addition, as 261 of the 292 fully evaluated cases were treated for cavity, there

are insufficient data on the use of phrenic nerve interruption in treating indications other than cavity, such as progressive disease or a persistently positive sputum.

The observed relationship of most of the factors studied above to results with phrenic nerve interruption confirmed established clinical judgment. It was clear that age, sex, and side of operation had essentially no bearing on results. On the other hand, the extent or intensity of the disease, as shown by roentgenogram; the size of cavity or cavities; the presence of homolateral endobronchial disease as directly visualized or as presumed from the presence of cavity with fluid level; and the extent and activity of disease in the contralateral lung; all were significantly related to results.

The relationship of cavity wall to results in general was as expected. Although thin-walled cavities responded most favorably, the 24 per cent final good results with thick-walled cavities is of interest. A cavity wall which appears thick by roentgenogram may be histologically (1) caseo-pneumonic, (2) fibrous and stiff, even epithelized, or (3) acutely infiltrated and/or relatively airless. Response of the latter type to various collapse measures is understandably better than the others and undoubtedly accounts for those good results with thick-walled cavities reported here.

There has not been much agreement as to the importance of location of the cavity or disease in determining results. Most authors have reported that they obtained best results in lower lobe lesions (5, 23, 38, 39, 40). A few others have noted good results where the lesion is situated in the apex of the lower lobe (41, 42), or the upper lobe (one group, 43). Alexander believes that the location of the lesion makes little difference (22) in determining the outcome from the procedure. This study supports the last opinion, with the additional finding that final results in basal lesions were poorer than in all other locations.

It is believed that sufficient evidence was obtained from this study to advise repetition of phrenicectomy as often as necessary to maintain a therapeutically successful hemidiaphragmatic paralysis for a considerably longer period than the average five to eight months' duration of an initial phrenicectomy. This was shown principally by the finding that total duration of paralysis, including repeat phrenicectomies, was significantly longer in the final good results than in the initial good results followed by relapse within three years and in the initial poor results. The relapses coincident with return of hemidiaphragmatic function provided additional support for this view. Just how long paralysis should be maintained is still uncertain, but the evidence would favor at least twelve to eighteen consecutive months of paralysis.

It has been previously pointed out that preoperative immobility of the hemidiaphragm has surprisingly little effect on results with phrenic nerve interruption (39). The limited observations made here confirm this view.

Some of the evidence in this study supports the contention that phrenic nerve interruption is an effective form of treatment for pulmonary tuberculosis. As observed by others (38, 40), a small group of patients responded remarkably well. Some had large, even multiple cavities, some were getting worse under observa-

tion, and others showed very heavy shadows or apparently quite old disease. All of these qualities are known to be associated with disease resistant to any treatment. In addition, a number of these unique unpredictable good results had failed to improve on six months or more of bed-rest immediately preoperatively. The close relationship of higher than average hemidiaphragmatic "rise" with the contraction and healing of such lesions also suggested that something positive had been accomplished by relaxation of the hemidiaphragm. Finally, the 26 instances of aggravation of disease coincident with return of hemidiaphragmatic function tend to support the view that the paralysis had been having a beneficial effect in those particular cases.

It may be contended, however, that the evidence obtained from this series fails to prove a wide effectiveness of the procedure. In the first place, the mean duration of postoperative sanatorium care in cases with initial good results was ten months, a not inconsiderable period. This figure was approximately the same regardless of whether relapse occurred later or not. The relapse rate after initially successful phrenic nerve interruption was 34 per cent at the end of the third year and 40 per cent in five years, compared to a recent report of 15 per cent relapses in the first five years after initially successful thoracoplasty (44). Comparable relapse rates after initially successful pneumothorax could not be found, but the available figures suggest that the relapse situation after pneumothorax is more favorable than these figures for phrenic nerve interruptions.

From table 8 it is seen that results were better in those patients who had had less of a trial on bed-rest before operation. In addition, there were only 27 patients who had a presumably adequate trial, *e.g.*, six months, of good bed-rest before operation and who then responded favorably to phrenic nerve interruption, an observation similar to that reported by Nordgren (39). How many of the other 67 final good results, with less than six months of consecutive preoperative bed-rest, would have done as well on bed-rest alone remains problematical. Further, the percentage of failure to control disease which was getting worse before operation was rather high (figure 6).

A careful study of all failures revealed many cases with a limited amount of improving or relatively recent disease, with small cavity and other favorable attributes, in which results were unaccountably poor. There seemed to be no explanation for these failures except possibly a high incidence of failure to obtain the greater degree of hemidiaphragmatic "rise" found rather consistently related to good results. This in turn suggested the unsuspected presence of pleural adhesions, parenchymal fibrosis and/or secondary emphysema which prevented adequate or selective relaxation.

A review of serial preoperative films in the unpredictably good results frequently revealed a progressive contraction of the diseased portion of lung, as evidenced by strand-like shadows radiating from the hilum, and retraction of mediastinal structures, ribs, hilum and hemidiaphragm. Study of the unaccountably poor results, on the other hand, showed that there was infrequent roentgenographic evidence of progressive preoperative pulmonary contraction. The importance of this factor of contraction was supported by the striking differ-

ence in degree of postoperative hemidiaphragmatic "rise" in the two groups. The less favorable results in the presence of extensive pleural adhesions, with a concomitant limitation in ability to contract, lends further support to this view (table 6).

The direct relationship found to exist between the height of the hemidiaphragm during paralysis and good results has been previously reported (12, 20, 39, 45) with one observer in dissent (38). The only positive force which can cause such a true "rise," as distinguished from fixation in the position of quiet expiration, is an acquired tendency of the diseased area to contract, long recognized as a reliable sign of spontaneous healing. In this connection, it has been previously emphasized that "contracting" (not entirely synonymous with improving) disease is in the most favorable state for success with pneumothorax and thoracoplasty (46).

#### SUMMARY

1. Of 398 patients subjected to phrenic nerve interruption for pulmonary tuberculosis from 1925 through November 1947, 292 "cases" provided adequate data for a detailed statistical study of the procedure.

2. Approximately one-half of these fully evaluated cases had an initial good result, while one-third remained well without relapse for three postoperative years. Results were slightly better for the temporary operations than for the permanent type.

3. Of the 94 final good results, only 27 had been given six months or more of bed-rest just prior to phrenic nerve interruption.

4. The relation of various factors to initial and final results was determined and discussed.

5. Cumulative relapse rates following initial good results with phrenic nerve interruption were 18 per cent in one and one-half years, 25 per cent in two years, 34 per cent in three years, 37 per cent in four years and 40 per cent in five years.

#### CONCLUSIONS

1. Phrenic nerve interruption is beneficial in certain cases of pulmonary tuberculosis and in well selected cases appears to provide a definitive form of treatment.

2. Because of the inadequacy of preoperative bed-rest and the absence of dependable controls, however, only limited evidence was found in the present study to support the belief that phrenic nerve interruption provides a widely effective form of treatment for the disease.

3. The most dependable guide to the selection of cases for phrenic nerve interruption in this series was the finding on serial roentgenograms, over a three- to six-month period, of progressive pulmonary contraction, as distinguished from simple clearing of disease or reduction in cavity size.

4. After hemidiaphragmatic paralysis has been effected, a good final result is more likely: (a) when significant hemidiaphragmatic "rise" occurs, preferably above the resting expiratory level; (b) when phrenic nerve interruption is repeated as often as necessary to maintain paralysis for from twelve to eighteen months.

## SUMARIO

*La Interrupción del Frénico en el Tratamiento de la Tuberculosis Pulmonar*

1. De 398 enfermos en quienes se ejecutó la interrupción del frénico por tuberculosis pulmonar desde 1925 hasta noviembre, 1927, inclusive, 297 "casos" aportaron datos adecuados para un pormenorizado estudio estadístico del procedimiento.

2. Aproximadamente en la mitad de estos casos bien justipreciados el resultado inicial fué bueno, en tanto que la tercera parte continuó bien sin recidivas durante tres años postoperatorios. El resultado fué ligeramente mejor con las operaciones temporales que con las permanentes.

3. De los 94 resultados definitivos buenos, sólo en 27 había habido seis meses o más de reposo en cama precisamente antes de la intervención en el frénico.

4. Se determinó y se discute ahora la relación de varios factores con los resultados iniciales y definitivos.

5. Los coeficientes acumulativos de recidivas consecutivas a buenos resultados iniciales representaron 18 por ciento en año y medio, 25 por ciento en dos años, 34 por ciento en tres años, 37 por ciento en cuatro años y 40 por ciento en cinco años.

*Conclusiones*

1. La interrupción del frénico resulta beneficiosa en ciertos casos de tuberculosis pulmonar, y, en casos bien seleccionados, parece constituir una forma definitiva de tratamiento.

2. Sin embargo, debido a la insuficiencia del descanso en preoperatorio cama y a la falta de testigos fehacientes, sólo se descubrieron en el estudio actual datos limitados que apoyen la creencia de que la interrupción del frénico ofrezca una forma ampliamente eficaz de tratamiento de la enfermedad.

3. El guía más fidedigno para la selección de casos para la interrupción del frénico en esta serie consistió en el hallazgo, en radiografías seriadas, durante un período de tres a seis meses, de contracción pulmonar progresiva, en contraposición al mero despejo de la enfermedad o disminución del tamaño de la caverna.

4. Una vez efectuada la parálisis hemidiafragmática, es más probable la obtención de un buen resultado definitivo: (a) si ocurre una importante "elevación" hemidiafragmática, preferiblemente más arriba del nivel expiratorio en descanso; (b) si es repite la interrupción del frénico con la frecuencia necesaria para mantener la parálisis por espacio de doce a dieciocho meses.

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# PERCENTAGE OF PERMANENT DIAPHRAGMATIC PARALYSES FOLLOWING PHRENICOTRIPSY<sup>1</sup>

JAMES T. HARDY, JR., WILLIAM H. BERGSTROM AND ROBERT H. BROWNING

## INTRODUCTION

In planning a program of treatment for an individual case of pulmonary tuberculosis, the risk of permanent diaphragmatic paralysis following crushing of the phrenic nerve (phrenicotomy) must often be considered. Such paralysis may compromise the patient's vital capacity and possibly preclude subsequent thoracoplasty or other necessary ipsilateral or contralateral collapse therapy. The value of phrenicotomy as an interim procedure depends, at least partially, upon its reversibility. The increasing use of phrenic nerve paralysis in combination with pneumoperitoneum has made this problem one of considerable interest and importance. With this in mind, the writers have reviewed a number of cases of patients who have had one or two phrenicotomies and have determined the percentage of partial and complete diaphragmatic paralysis resulting.

## REVIEW OF LITERATURE

There have apparently been very few studies of this subject. Mitchell et al. (1) studied 193 patients who had had one phrenicotomy followed by pneumoperitoneum. After one to four years, 42 per cent of these showed complete paralysis and 9.5 per cent partial paralysis of the diaphragm. In a parallel series of 192 initial phrenic crushes alone, performed by the same surgeons, some with pneumothorax but without coincident pneumoperitoneum, 21.3 per cent showed complete and 16.1 per cent partial failure to regain normal function in from one to four years after crush.

Crow and Whelchell (2), in studying 546 patients who had had phrenicotomy and pneumoperitoneum, found 5 per cent permanent diaphragmatic paralysis.

Pinner (3), without citing specific figures, estimated that 10 per cent of supposedly temporary diaphragmatic paralyses are in reality permanent.

## MATERIAL AND METHOD

In this study no patients were used who might have restriction of diaphragmatic motion caused by pleural thickening, effusion, empyema, or peritonitis. Three categories were established: (1) complete paralysis; (2) partial paralysis, meaning any motion in the normal direction up to two centimeters; (3) no paralysis, meaning motion in the normal direction of more than two centimeters. All cases considered were classified by fluoroscopy two years or more after operation. All paralyses which remained for two years were arbitrarily considered to be permanent. No patient was included whose contralateral diaphragm moved less than two centimeters at the time of classification. All patients received concurrent pneumoperitoneum.

<sup>1</sup> From Sunny Acres, Cuyahoga County Tuberculosis Hospital, Cleveland, Ohio, and the Department of Medicine, Western Reserve University School of Medicine.

*Operative technique:* The operative technique used was as follows. Under local anesthesia the nerve was approached via a muscle-splitting incision in the lateral head of the sternocleidomastoid. In each case a thorough search for accessory nerves was made. These were severed if found. The nerve was then injected with 2 per cent pontocaine and crushed seven to nine times at one point with a hemostat. The muscle was then apposed with chromic sutures and the skin with silk. Each patient was then fluoroscoped. Those whose diaphragms were found to be moving following operation were excluded from the series.

TABLE 1  
*Reduction of diaphragmatic function following phrenicotomy*

|                                      | CASES WITH ONE CRUSH (143) |          | CASES WITH TWO CRUSHES (49) |          |
|--------------------------------------|----------------------------|----------|-----------------------------|----------|
|                                      | Number                     | Per cent | Number                      | Per cent |
| Partial paralysis.....               | 7                          | 5        | 6                           | 12       |
| Complete paralysis.....              | 14                         | 10       | 6                           | 12       |
| Total cases with reduced function... | 21                         | 15       | 12                          | 24       |

### RESULTS

As may be seen in table 1, 143 cases of phrenicotomy were reviewed. Of this number, 7, or 5 per cent, had partial paralysis of the diaphragm on the operated side two years or more after the procedure. Fourteen cases, or 10 per cent, had complete paralysis. This gives a total of 21 cases, or 15 per cent, who had appreciable and apparently permanent compromise of their diaphragmatic function.

A total of 49 cases having two phrenicotomies was considered. All of these had shown return of diaphragmatic function following the first operation. Six cases, or 12 per cent, showed partial paralysis two years after the second operation. Six cases, or 12 per cent, showed complete paralysis. Thus 12 cases, or 24 per cent, were found to have permanent reduction of diaphragmatic function after their second phrenicotomy.

Though the number of cases having two operations (49) is small as compared with the number having one operation (143), application of the Chi-Square method shows that in only 7 per cent of such samples would there be more divergent results.<sup>2</sup>

### DISCUSSION

Two factors may be involved in permanent diaphragmatic paralysis: (1) failure of the phrenic nerve to regenerate; and (2) muscle atrophy in the diaphragm itself. The relative importance of these factors remains to be deter-

<sup>2</sup> Acknowledgment is made to Mr. John L. Buckley of the University of Syracuse, who prepared the statistical analysis of our data.

mined. Stanbury (4) found profound gross and microscopic changes in the diaphragm in 10 cases autopsied from three weeks to six years following phrenicectomy. He described moderate changes as early as three weeks postoperatively, and his description of the findings at four months is as follows: "The entire musculature undergoes atrophy, leaving a thin fibrous structure. Histologically, fatty degeneration is present, an occasional atrophic muscle cell may be seen, and the fibrous element is much thinner than normal."

The figures in the present study indicate a considerably higher proportion of permanent reduction of function following second crushes as compared to first crushes. At operation for re-crush much local fibrosis is invariably found and the nerve is frequently isolated only with great difficulty. It seems possible that scarring, by preventing nerve regeneration, may account for the high percentage of permanent paralyses observed. Stanbury's figures would seem to indicate, however, that muscle atrophy may occur very early and this might be as important a factor as failure of nerve regeneration. If the latter were the more important, any technique which would paralyze the nerve with minimal scarring might lead to a higher percentage of recovery of function. Crow and Whelchell (2) recommend dissection of the nerve from its sheath and crushing of the nerve only. In a series of 546 cases they report only 5 per cent permanent paralyses.

With the foregoing in mind, it would seem desirable that a series of diaphragms and phrenic nerves be examined postmortem in an effort to draw definite conclusions as to the importance of these factors.

#### SUMMARY

1. A series of cases having phrenicotripsy and pneumoperitoneum was reviewed two years or more postoperatively. Fifteen per cent of 143 cases had permanent reduction of diaphragmatic function after the first operation. After a second phrenicotripsy, 24 per cent of 49 cases showed permanently reduced function.

2. The relative importance of nerve regeneration and muscle atrophy is discussed and it is believed that further studies, both statistical and histological, are indicated.

#### SUMARIO

##### *Porcentaje de Parálisis Diafragmáticas Permanentes Consecutivas a la Frenicotripsia*

1. Una serie de casos en que se practicaron la frenicotripsia y el neumoperitoneo fué repasada a los dos años o más de la operación. En 15 por ciento de 143 casos hubo reducción permanente de la función diafragmática después de la primera operación. Después de otra frenicotripsia, 24 por ciento de 49 casos mostraron disminución permanente de la función.

2. Discútese la relativa importancia de la regeneración nerviosa y la atrofia muscular, señalándose que parece indicada la ejecución de estudios ulteriores, tanto estadísticos como histológicos.

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# PSYCHOLOGICAL CONCOMITANTS OF PULMONARY TUBERCULOSIS<sup>1</sup>

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## INTRODUCTION

### *Statement of the Problem*

For many years the question of whether there are specific personality changes accompanying tuberculosis has aroused speculation and discussion. Those inclined to answer the question in the affirmative have pointed to such men as Schiller, Voltaire, Shelley, and others, as evidence for the theory that tuberculosis is a factor in producing heightened creativity along intellectual lines. Thomas Mann's novel, *The Magic Mountain* (8), brought widespread attention to the lives of those afflicted with the disease and has done much to shape the thinking of many about tuberculosis.

Recent work in psychosomatic medicine and in the organismic approach to the individual has shown that the whole organism and hence the total behavior pattern reacts to any infection.

Little work of a rigidly controlled nature has been done to determine whether there are demonstrable personality concomitants to tuberculous infection. Much of the literature on the subject is the product of subjective observation and clinical experience. As a result there are many conflicting and divergent assertions as to personality changes with tuberculosis. Moreover, as it is probable that many clinicians have compared their tuberculous patients with healthy people in their regular environments, it is difficult to know whether the traits they ascribe to the tuberculous patients are specific to that disease or are rather only typical of chronic illnesses in general.

This study purports to obtain quantitative measures of personality factors in a group of tuberculous patients and in a comparable group of chronically ill nontuberculous patients so that a comparison of the two groups may be made. An attempt also is made to see whether there are any correlations between the severity of infection, objectively determined, and the degree of deviation from the normal in personality factors, if such deviations occur.

### *Survey of the Literature*

The widely divergent opinions about personality changes with tuberculosis are evident from the following references which are a representative sample of the literature.

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Moorman (10) says, "After allowing for the increased mental activity which is apt to accompany enforced physical rest, and the fear of impending death, many students of tuberculosis have expressed the belief that there is a decided excitation of the mind with increased capacity for creative accomplishment and that this excitation is due to toxic agents manufactured by the tubercle bacillus."

In support of this view, Thompson (19) is led to say, "I do not believe tuberculosis is a clinical entity in the causes of insanity *per se*, but rather that the toxic element may so undermine patients' psychic equipment as to produce mental symptoms."

Jelliffe and Evans (7) believe that the chronic toxemia of tuberculosis is irritating to nerve cells and produces a general disharmony in the cellular activity.

Hayes (5) says that the centers of nervous and mental control of tuberculous patients are affected by the poisons of the disease and that therefore these patients are not only physically but also nervously and mentally ill.

Shock and Jones (15) disagree with the above contentions and argue that the simple assumption that any changes in personality accompanying tuberculosis are a result of heightened motivation in the face of the imposed inactivity and physical handicaps is more reasonable than the hypothesis that there are specific poisons which act as excitants to the central nervous system.

In a survey of the literature on the emotions of tuberculous patients, Shutz (16) outlines three divergent points of view which are current in relation to the problem. These are, first, that there is a toxic condition which causes personality changes; second, that patients' bodily states are influenced by emotions and vice versa; and third, that cultural and socio-economic conditions have adversely affected the lives of the patients, with accompanying emotional changes. He concludes that the sanatorium population is more emotionally maladjusted than the general population but no more so than in other conditions which act to produce emotional crises. He says that more recent authors believe that tuberculosis merely accentuates personality maladjustments present prior to infection.

Hartz (3) points out that such reactions as anxiety states, which occur as a result of life situations, may so disrupt the normal pattern as to be an important factor in the onset of tuberculosis. He points out, however, that these reactions will differ from individual to individual so that no generalized pattern is likely to exist.

Seidenfeld (13) does not believe that we have enough knowledge to say whether the psychic components are causative of, or reactions from, the illness, but he stresses the presence of these components and the necessity for understanding and training tuberculous patients so that upon discharge they may take their place in society.

Hyde and Zacks (6) found correlations between population density and incidence of tuberculosis for communities above 5,000 per square mile and thought the correlations were due to crowding *per se*, and not to lower socio-economic status or nationality.

Several attempts have been made to show that definite psychoses, particularly schizophrenia, are caused by tuberculosis. In fact the incidence of tuberculosis in schizophrenics is much higher than in all of the other mental illnesses. As Dunbar (2) has pointed out, these attempts are derived from the statistical coexistence of the two illnesses. She believes that schizophrenic patients have lower resistance to infection and succumb more easily than others. White (21) concurs with this view. Ruskin (12), in a survey on epidemiology of tuberculosis in a mental hospital, says that probably susceptibility to the illness is not related to the type of mental disorder except that some mental disorders require longer hospitalization and that infection is a result of overcrowding and carelessness in matters of personal hygiene.

In a psychoanalytic investigation of thirty tuberculous women, Muhl (11) found numerous and varied personality characteristics which she believed resulted from the illness. Among these were changes in sexuality, impairment of the "ethical sense," cyclic emotions, and dissociative trends.

Strecker, Braceland, and Gordon (18), after studying 2,000 patients psychologically and seventy-five very intensely, were unable to find any evidence for euphoria or increased sexual desire. They did find evidence for depression and anxiety.

Weigel (20) in a study of two hundred patients found that forty-seven per cent were suffering from a definite psychosis or neurosis. The majority of these were hysterics and neurasthenics. He concludes that functional nervous illness occurs with great frequency and that a neuropsychiatric state can be a predisposing factor in tuberculosis. He believes also that psychiatric treatment is important and that the neurotic has a worse prognosis than the patient with a normal personality.

Seidenfeld (14), in a comparison of tuberculous patients with normals, found that fifteen of the one hundred questions in the Maller Personality Sketches distinguished significantly between the groups. Eight of the discriminating questions related to mental health, and the rest dealt with personal adjustment, self-control, habit patterns and social adjustment.

Shutz (17) found differences between tuberculous patients and the general norms on the Bernreuter Personality Inventory in that the former were more neurotic, more lacking in self-sufficiency and self-confidence, more introverted, more submissive, and more gregarious.

As will be evident from the statements and assertions made above, there is no consistent agreement as to what the psychological concomitants to tuberculosis actually are. Neither is there agreement about whether subjectively or objectively observed differences are results of the disease, are predisposing factors to the disease, or are merely accentuated by the stress of illness.

The complete literature is not reviewed here. Rather, a number of studies are referred to which give a sample of opinion in several areas of thought about tuberculosis. One of the factors giving impetus to the present study is the confusion evident in the literature on the subject. Much of the discussion of the problem is the result of subjective impression and clinical experience. Thus, Lawrenson Brown (1) concludes in a survey of the literature, "Contradiction contradicts contradiction, and the tuberculous patient is described as anything between an insane criminal and a saint too ethereal for this mundane sphere. Few articles have been based on recorded observation, and many upon the imagined experience of the writer."

#### MATERIAL AND METHODS

Two groups, one composed of patients diagnosed as having active pulmonary tuberculosis and another composed of chronically ill nontuberculous patients, were administered the Minnesota Multiphasic Personality Inventory (hereinafter called the MMPI). The groups were equated as nearly as possible with regard to age and intelligence. Both groups were composed of veterans being treated in Deshon Veterans Administration Hospital, Number 5175, Butler, Pa. The MMPI and the Otis Self-Administering Test of Mental Abilities, Higher

Form A, were given to both groups under similar conditions. The twenty minute form of the Otis was used. Results of this test, which will be called Otis I.Q.'s, were used to compare the two groups in intelligence. As indicated in the test manual, these scores should not be considered true intelligence quotients but give results which are adequate for equating the groups.

The control group of nontuberculous patients with chronic illnesses was composed of veterans diagnosed as having demonstrable arthritis, demonstrable ulcer, and severe cardiac disturbances. An analysis of variance was computed and indicated that these subclasses comprising the control group did not vary significantly in mean T-scores for any of the scales on the MMPI. It was felt to be justifiable to combine these groups into one control group as they all had in common a restricting illness which limited their activity, necessitated much bed-rest, and required long hospitalization. No denial of the possibility of serious psychosomatic factors in these illnesses is implied, but a comparison of tuberculous patients with this group was felt to be justified in order to ascertain whether there were any specific personality factors measured by the MMPI which would be specific to the tuberculous group and not to the control group.

The tuberculous patients were classified into four groups by the ward surgeons according to the severity of infection. Correlations between the severity of infection and deviations on the MMPI were computed.

Means, standard deviations, and standard errors of means for each of the nine scales of the MMPI were computed for the experimental and control groups. Critical ratios utilizing Student's "t" were then computed to determine the amount and nature of differences between the groups.

The diagnosis of pulmonary tuberculosis was made on the basis of laboratory studies which included roentgenograms and examination of sputum and gastric washes. Only pulmonary tuberculous infections are included in the study. On the basis of the above diagnostic methods, the patients were classified by ward surgeons into a four class scale ranging from most severe to least severe infection.

The diagnosis of arthritis was made on the basis of roentgenograms and clinical examination. As the patients used in this study were from a young age group, they were nearly all rheumatoid arthritides. The ulcer group was diagnosed on the basis of roentgenographic and clinical study. Only demonstrable peptic ulcer patients are included. The diagnosis of cardiac disease was based on clinical observation and only those with definite cardiac disturbance are included.

### *Measurement of Personality Disturbance*

The Minnesota Multiphasic Personality Inventory (4) is a questionnaire in booklet form, consisting of 566 items, which purports to give a quantitative measurement of personality in nine areas. These areas, each determined by a separate scale, are: *hypochondriasis, depression, hysteria, psychopathy, masculinity-femininity, paranoia, psychasthenia, schizophrenia, and mania*.

In addition to these scales, there are included certain validating scales which are used to determine, as far as possible, whether a subject understands the items, whether he is lying, and whether he is omitting questions in numbers sufficient to alter his scores. These scales are called the F-scale, the L-scale, and the Q-scale (4).



Recently an additional factor, called the K-factor, has been established statistically which, when applied to the test results, corrects the tendency to be defensive, to put oneself in a too favorable light or the opposite, to be exceptionally self-critical (9).

All of these validating scales were used in the present study.

### *Treatment of Data*

An analysis of variance for the three subclasses (arthritis, peptic ulcer and cardiac disease) comprising the control group was computed. The results indicated that these subclasses did not vary significantly in mean T-scores from each other. The F-scores for two of the scales, schizophrenia and mania, were significant but, as the means of the subclasses in these two scales were within a decimal fraction of each other, it may be inferred that it was the variability of distribution of these subclasses which caused the high F-score. As a result of the lack of variation between the means of these subclasses, they were combined to form one control group.

Next, the mean chronological ages, standard deviations, and standard errors of means for the control and experimental groups were determined. These statistics were used to compute a critical ratio. A difference of 3.12 years between means is significant at the one per cent level of confidence. This same procedure was then applied to the Otis I.Q. scores. Here a difference of 2.09 between the means of the two groups is not significant.

The record blanks for the MMPI were scored and these scores converted into T-scores using the revised norms which included correction for the K-factor (22). The mean T-scores for each of the groups, together with the standard deviations, standard errors of means, and standard errors of differences between means were determined for each of the nine scales of the MMPI. From these data, critical ratios between mean T-scores on each of the scales were computed and examined for significance at the one and five per cent levels of confidence, taking into account the appropriate degrees of freedom and using Student's "t."

Linear correlations between the T-scores of tuberculous individuals on each of the scales and their classification according to severity of infection (classification described above) were calculated.

## RESULTS

### *Age and Intelligence*

The average age of the tuberculous group was approximately three years less than that of the nontuberculous group. This difference is significant at the one per cent level of confidence. It was felt, however, that this difference had little significance in the context of the present study for the groups were equated for a number of other factors, including sex, veteran status, chronic illness, hospitalization, and intelligence. The tuberculous group is approximately two scale points higher in intelligence than the nontuberculous group. This difference is not statistically significant. The actual means and standard deviations obtained for the two groups in these factors are presented in table 1.

### *Results on the MMPI*

The mean T-scores on each of the nine scales of the MMPI for both the tuberculous and nontuberculous groups are consistently higher than the mean T-scores for the general population, which on this test are fifty. In table 2 are

presented means and standard deviations on the nine scales for the groups studied.

### *Differences between the Groups*

The computation of critical ratios between the groups for each scale of the MMPI indicates that there are significant differences between tuberculous patients and other chronically ill patients. Critical ratios that are significant at

TABLE 1

*Means and standard deviations in chronological age and Otis I.Q. for groups studied*

|                           | NUMBER | MEAN C. A. | S.D. | MEAN OTIS I.Q. | S.D.  |
|---------------------------|--------|------------|------|----------------|-------|
| Tuberculosis group.....   | 52     | 26.96      | 5.77 | 104.76         | 10.95 |
| Nontuberculous group..... | 61     | 30.08      | 7.07 | 102.67         | 10.76 |

TABLE 2

*Mean T-scores and standard deviations for scales of the Minnesota Multiphasic Personality Inventory for groups studied*

| SCALE                       | TUBERCULOUS PATIENTS |       | NONTUBERCULOUS PATIENTS |       |
|-----------------------------|----------------------|-------|-------------------------|-------|
|                             | Mean                 | Sigma | Mean                    | Sigma |
| Hypochondriasis.....        | 65.79                | 13.66 | 71.00                   | 13.57 |
| Depression.....             | 63.12                | 10.76 | 67.98                   | 12.25 |
| Hysteria.....               | 61.94                | 10.59 | 65.77                   | 11.18 |
| Psychopathy.....            | 63.33                | 12.49 | 59.05                   | 10.39 |
| Masculinity-femininity..... | 56.31                | 9.60  | 51.90                   | 7.21  |
| Paranoia.....               | 52.81                | 10.18 | 52.26                   | 9.00  |
| Psychasthenia.....          | 58.79                | 11.95 | 56.33                   | 11.36 |
| Schizophrenia.....          | 58.17                | 10.63 | 57.61                   | 14.63 |
| Mania.....                  | 62.23                | 9.24  | 54.69                   | 8.72  |

the one per cent level of confidence were found on the manic Scale and on the masculinity-femininity Scale. This is in the direction that indicates that tuberculous patients are more hypomanic and more feminine than are other chronically ill patients. Critical ratios that are significant at the five per cent level of confidence were found on the hypochondriasis and depression scales. These were in the direction that indicates that tuberculous patients are less hypochondriacal and less depressed than other chronically ill patients. The "t" values for these critical ratios are presented in table 3.

The percentage of each group falling above a T-score of seventy, which has been designated as being outside normal limits, is shown in table 4. Only those scales in which significant differences were found are presented.

### *Correlations between Severity of Infection and T-scores on MMPI*

The calculation of correlation coefficients between severity of infection and T-scores on each of the scales indicated that there was no relationship between

these factors in the present data. All of the correlation coefficients were between  $-.10$  and  $.10$  and were not significant.

### DISCUSSION

From the results reported above, some suggestions as to the psychological concomitants of tuberculosis may be advanced. In comparing the results of patients' answers to the items of the MMPI with the norms for the general population, it may be said that the chronically ill, and therefore the tuberculosis patient, show scores in the direction of maladjustment on each of the scales.

TABLE 3

*"t" Values between tuberculosis and control groups for data presented in table 2*

| SCALE                       | "T" VALUE |
|-----------------------------|-----------|
| Hypochondriasis.....        | 2.01*     |
| Depression.....             | 2.22*     |
| Hysteria.....               | 1.86      |
| Psychopathy.....            | 1.95      |
| Masculinity-femininity..... | 2.71†     |
| Paranoia.....               | 0.30      |
| Psychasthenia.....          | 1.11      |
| Schizophrenia.....          | 0.23      |
| Mania.....                  | 4.41†     |

\* Significant at 5 per cent level.

† Significant at 1 per cent level.

TABLE 4

*Per cent of each group falling above T-score of 70 on Minnesota Multiphasic Personality Inventory for scales showing significant differences*

| SCALE                       | TUBERCULOUS GROUP | NONTUBERCULOUS GROUP |
|-----------------------------|-------------------|----------------------|
|                             | <i>per cent</i>   | <i>per cent</i>      |
| Mania.....                  | 19                | 7                    |
| Masculinity-femininity..... | 13                | 0                    |
| Hypochondriasis.....        | 38                | 54                   |
| Depression.....             | 31                | 48                   |

The means for the chronically ill on these scales are almost entirely within the range designated as normal limits, but the elevation of T-scores indicates that there are more individuals in these groups who fall outside normal limits than there are in the general population. The percentage distributions for each of the groups and the per cent falling above a T-score of seventy, are illustrated graphically in figures 1, 2, 3, and 4.

In comparing the experimental group with the control group it was found that tuberculous patients are more hypomanic and more feminine than nontuberculous chronically ill patients; it was also found that they are less depressed and less hypochondriacal than nontuberculous patients.

From these results it may be concluded that there is some objective basis for postulating the existence of the often referred to "euphoria" in tuberculosis. The most significant difference in the present study was on the manic scale.

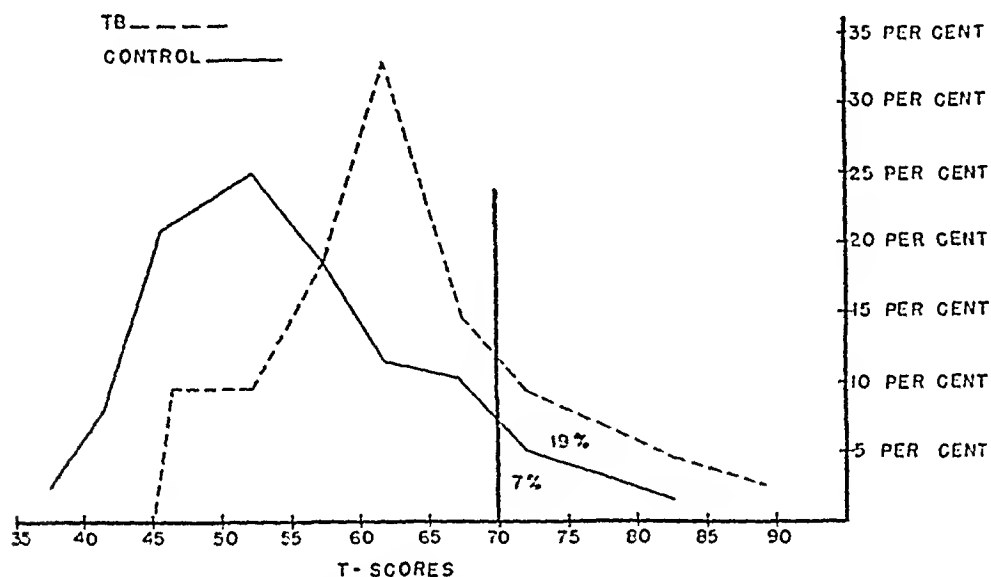


FIG. 1. Percentage distribution of the tuberculous and control groups on the manic scale of the Minnesota Multiphasic Personality Inventory.

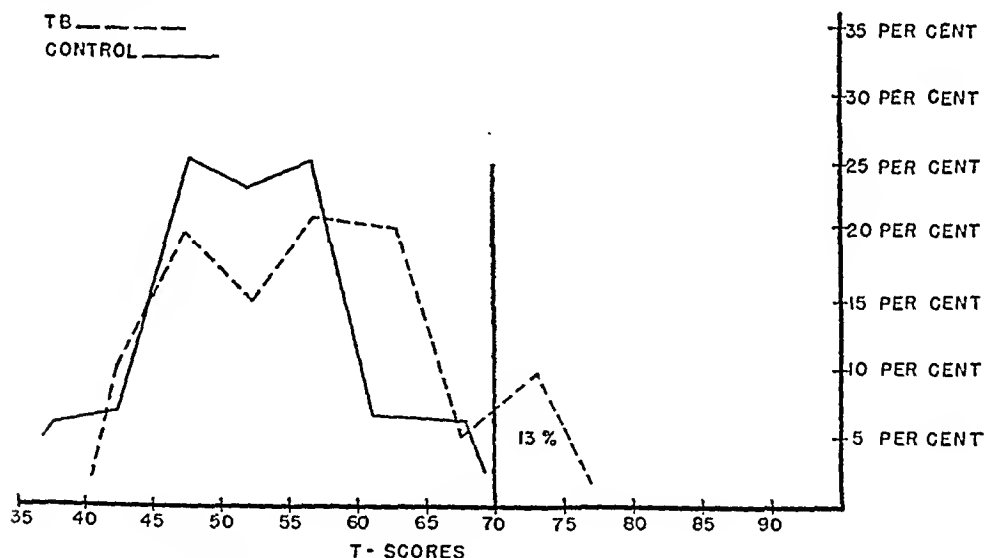


FIG. 2. Percentage distribution of the tuberculous and control groups of masculinity-femininity scale of the Minnesota Multiphasic Personality Inventory.

The difference in masculinity-femininity is also highly significant, although the mean T-score for the tuberculous patients is well within normal limits.

The following suggested explanation of these results is advanced, although only tentatively because of the size of the present sample. Tuberculous pa-

tients are in less acute discomfort due to their illness than are the other patients studied. It is possible that their lack of physical discomfort, together with

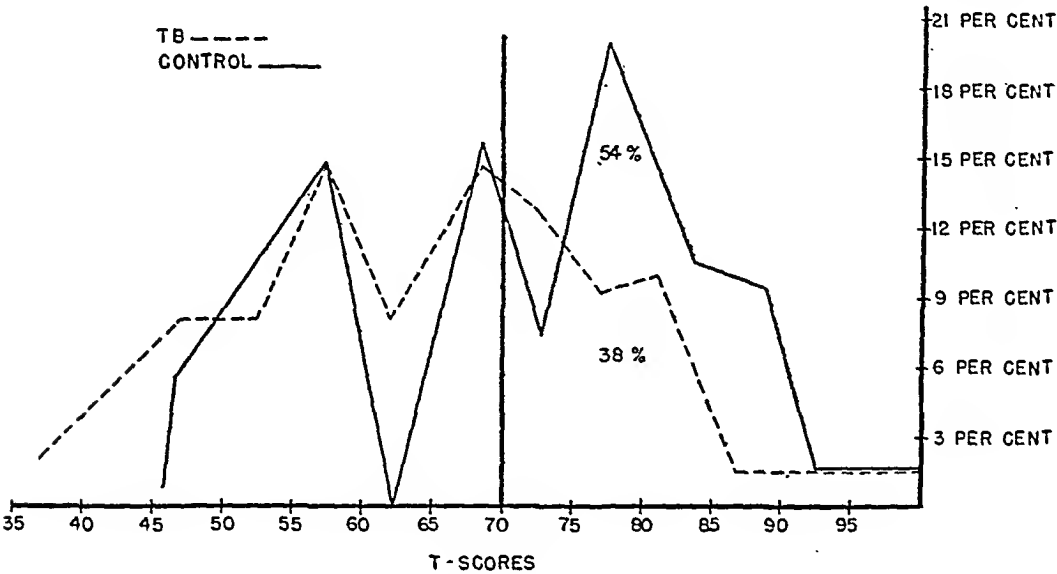


FIG. 3. Percentage distribution of the tuberculous and control groups on the hypochondriasis scale of the Minnesota Multiphasic Personality Inventory.

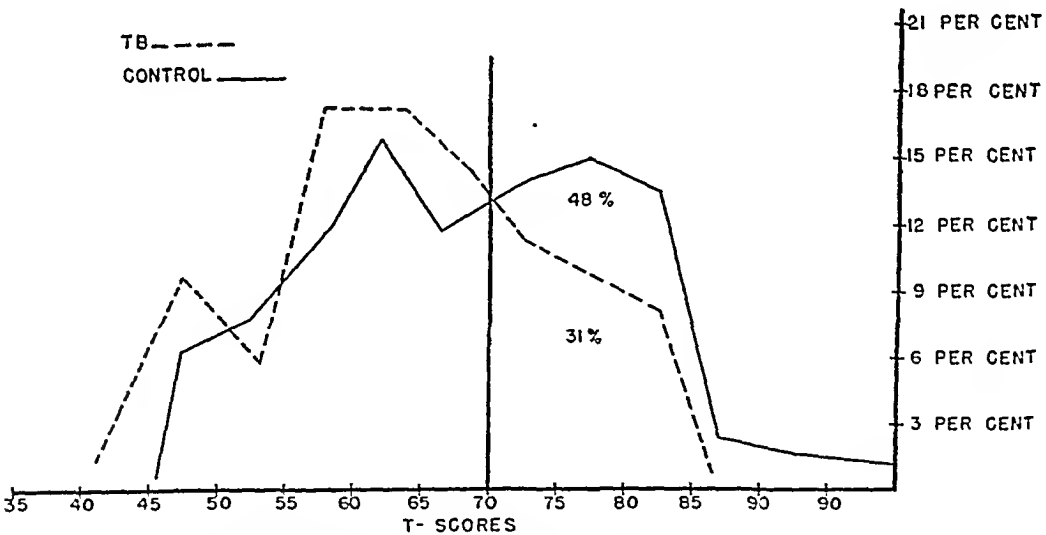


FIG. 4. Percentage distribution of the tuberculous and control groups on the depression scale of the Minnesota Multiphasic Personality Inventory.

their enforced bed-rest, their highly nutritious diet including high vitamin intake, and their isolation from normal recreational pursuits, all combine to produce psychological drive to activity. The frustration to release of this drive only enhances its potency with a resultant state of hyperexcitability which is labeled

euphoria. From this hypothesis also would follow the lower scores on depression and hypochondriasis. Because they feel better and have less physical discomfort than other patients, they are less preoccupied with physical symptoms not directly related to their progress toward recovery.

The higher femininity score may be a situational reaction to conditions under which they are frequently more dependent on nursing and medical attention than are other patients.

This explanation is felt to be more parsimonious than others which attribute emotional symptoms to actual poisons from the tubercle bacillus itself. Also the lack of correlation between the severity of emotional disturbance and severity of infection, though on a small population, argues against the latter theory.

#### SUMMARY

Two groups, one composed of veterans with pulmonary tuberculosis and the other composed of veterans with chronic illnesses other than tuberculosis, were used in the present study. The groups were equated as far as possible for intelligence, age, sex, hospitalization, chronic illness, and motivation.

The Minnesota Multiphasic Personality Inventory was administered to both groups.

The following results are indicated:

(1) Chronically ill patients in general deviate in the direction of maladjustment on each of the scales of the MMPI.

(2) The tuberculous patients were found to be significantly more hypomanic and more feminine than other chronically ill patients.

(3) The nontuberculous patients were found to be more depressed and more hypochondriacal than the tuberculous patients.

(4) No linear relationship between degree of emotional deviation and severity of tubercular infection was found to exist in the present data.

It is felt that the differences found can be explained by the hypothesis that tuberculous patients are made less uncomfortable by their illness than are other chronically ill groups. This, together with their nutritious diet and frustration to normal activity, combine to produce a state of heightened responsiveness which has been labeled euphoria. This explanation would also account for their lower scores on hypochondriasis and depression.

#### SUMARIO

##### *Concomitantes Psicológicos de la Tuberculosis Pulmonar*

Para el estudio actual utilizáronse dos grupos: uno compuesto de veteranos con tuberculosis pulmonar y otro de veteranos con enfermedades crónicas, distintas de la tuberculosis. Los grupos fueron igualizados en todo lo posible con respecto a inteligencia, edad, sexo, hospitalización, cronicidad de la enfermedad y móviles.

En ambos grupos se ejecutó el Inventario de la Personalidad Multifásica de Minnesota.

Los siguientes resultados quedan indicados:

(1) Los enfermos crónicos en general se desvían en sentido de desajuste en todas las escalas del IPMM.

(2) Los tuberculosos se mostraron significativamente más hipomaniacos y más femeninos que los otros enfermos crónicos.

(3) Los no tuberculosos se mostraron más deprimidos y más hipocondriacos que los tuberculosos.

(4) Los datos acopiados no revelaron ninguna relación lineal entre la intensidad de la desviación afectiva y la gravedad de la infección tuberculosa.

Parece que las diferencias descubiertas pueden explicarse por la hipótesis de que a los tuberculosos los molesta más la enfermedad que a otros enfermos crónicos. Esto, unido a su dieta nutritiva y falta de actividad normal, produce un estado de hipersensibilidad que se ha rotulado con el nombre de euforia. Esa teoría también explicaría los menores coeficientes de hipocondría y depresión en los tuberculosos.

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# THE RELATIONSHIP BETWEEN PHAGOCYtic CELLS AND HUMAN TUBERCLE BACILLI<sup>1</sup>

HUBERT BLOCH<sup>2</sup>

## INTRODUCTION

Although it has long been known that tubercle bacilli are readily phagocytosed even in susceptible hosts, no unequivocal information is available concerning their further fate within the phagocytes. There is some evidence that the bacilli exert an injurious effect on these cells (1, 7, 11, 18, 19, 20), but the significance of this effect in the establishment and progression of the infection remains obscure. Most studies dealing with the interactions between tubercle bacilli and leukocytes have been aimed at recognizing differences in the leukocytic response between susceptible and immune animals (5, 12, 16, 21).

The specific histological lesion of tuberculosis, the tubercle, can be produced by dead bacilli, by chemical fractions of bacilli, and even by some synthetic fatty acids. Thus, one of the most characteristic host responses is independent of the living functions and of the virulence of the parasite. Furthermore, attenuated or avirulent variants can under proper conditions cause lesions similar to those produced by virulent bacilli (8, 14). Although avirulent variants of *M. tuberculosis* thus possess some factors which play a part in pathogenicity, it is obvious that other factors are essential to the establishment of the infection as these variants cannot produce progressive tuberculosis in susceptible animals.

The purpose of the present study was to compare the effect of virulent and avirulent forms of human tubercle bacilli on leukocytes during the initial stage of the infection in the hope of recognizing differences which might have a bearing on the property of virulence. Indirect evidence has been obtained that the virulent bacilli can exert on polymorphonuclear cells a toxic effect, which results in leukocytolysis.

## EXPERIMENTAL

Male albino mice of the Rockefeller albino strain were used (15). They were infected by the intraperitoneal route. The susceptibility of these animals to tuberculous infection has previously been described (15). The experiments were carried out with two variants of the human strain of tubercle bacillus H37Rv, virulent, and H37Ra, avirulent.<sup>3</sup> The micro-organisms were grown for one week in the Tween 80-albumin medium (4). They were then separated by centrifugation and resuspended in fresh medium.

Uniform suspensions were thus obtained, which consisted of single cells or small agglomerates in the form of clumps or of "cords", depending upon the virulence of the culture (13). Heavy suspensions containing approximately 0.1 mg. dry weight bacilli per ml. were injected in amounts of 1.0 ml. per mouse.

<sup>1</sup> From the Laboratories of the Rockefeller Institute for Medical Research.

<sup>2</sup> Fellow of the Swiss-American Center for Medical Exchange and Information.

<sup>3</sup> These strains were originally obtained through the courtesy of Mr. W. Steenken of the Trudeau Sanatorium. They have been subcultured in our laboratory in the Tween-albumin medium.

The following determinations were made: (1) number of phagocytic cells in the exudate with and without engulfed tubercle bacilli; (2) number of free and intracellular tubercle bacilli in the exudate; (3) number of bacilli within the individual phagocytic cells.

Attempts were made to obtain repeated samples of exudate from the same mouse in order to carry out the determinations at different intervals of time after injection of the bacilli. More satisfactory results were obtained, however, by the following method.

Mice were killed at different intervals of time after infection and the peritoneal cavity was washed with 0.5 to 1.0 ml. amounts of a sodium citrate solution buffered at pH 6.9 and containing 1 per cent glucose. Preparations of peritoneal washings of even density were stained by the Ziehl-Neelsen and Giemsa techniques. In order to obtain comparable aliquots of peritoneal exudate care was taken that the fixed omental cells be removed in roughly comparable amounts. One hundred to 200 leukocytes or bacilli were counted on each slide. Serial repetition of the same experiment gave reproducible results and the data presented in the tables represent average values of at least five parallel experiments.

*Initial Exudate:* The initial exudate consisted chiefly of polymorphonuclear leukocytes. Monocytes represented less than 10 per cent of the total white cells during the first five hours. As the results to be described deal chiefly with the course of infection during this period of time, they apply only to polymorphonuclear cells.

*Phagocytic index of the exudate:* The experimental results summarized in table 1 give the percentage of leukocytes containing tubercle bacilli at different intervals of time after injection of bacilli. They reveal that both virulent and avirulent bacilli are phagocytosed readily by the leukocytes of the exudate. The slight decrease in phagocytic index observed during the later stages of these experiments in the mice infected with avirulent organisms may be significant as it is consistent with observations to be discussed later.

It will be noted that even at the very beginning of the experiment, when bacilli greatly outnumber the leukocytes in the exudate, only about 10 per cent of the total leukocytes show phagocytic activity. The findings in these early stages clearly indicate that there is no difference whatsoever in primary leukotactic activity between virulent and avirulent bacilli.

*Quantitative relation between free and phagocytosed tubercle bacilli in the exudate:* The results summarized in figure 1 illustrate that at the beginning of the experiment both virulent and avirulent bacilli are taken up at the same rate by the phagocytes but that differences become manifest some four hours after infection. From then on, the exudates of mice injected with virulent organisms contain more free bacilli than those of animals having received the avirulent variants.

*Quantitative distribution of phagocytosed bacilli within phagocytic cells:* As the bacillary suspensions used for intraperitoneal injections consisted not only of single bacilli but also of small clumps or "cords", the phagocytes could engulf one or more micro-organisms at once. In figures 2 and 3, which are the mean of 10 parallel experiments, are summarized the numbers of virulent and avirulent tubercle bacilli seen within the white cells of the exudate at different intervals of time after infection. Intracellular bacilli were easily demonstrable within the first five hours.

The polymorphonuclear leukocytes constitute more than 90 per cent of the exudate cells at the beginning of the infection. In mice infected with virulent

TABLE 1  
Per cent of leukocytes which engulfed bacilli in the peritoneal exudates of mice inoculated with virulent (H37Rv) and avirulent (H37Ra) tubercle bacilli  
The figures represent average values of 5 or more experiments

| HOURS AFTER INOCULATION | PER CENT OF PHAGOCYTTIC LEUKOCYTES IN THE EXUDATE OF MICE INOCULATED WITH |          |
|-------------------------|---|----------|
|                         | H37Ra   | H37Rv    |
|                         | per cent  | per cent |
| 1                       | 9   | 11       |
| 2                       | 16  | 17       |
| 3                       | 10  | 10       |
| 4                       | 7   | 13       |
| 5                       | 9   | 11       |
| 10                      | 7   | 8        |
| 15                      | 11  | 13       |
| 20                      | 6   | 9        |
| 48                      | 3   | 10       |
| 96                      | 1   | 15       |
| 192                     | 0   | 7        |

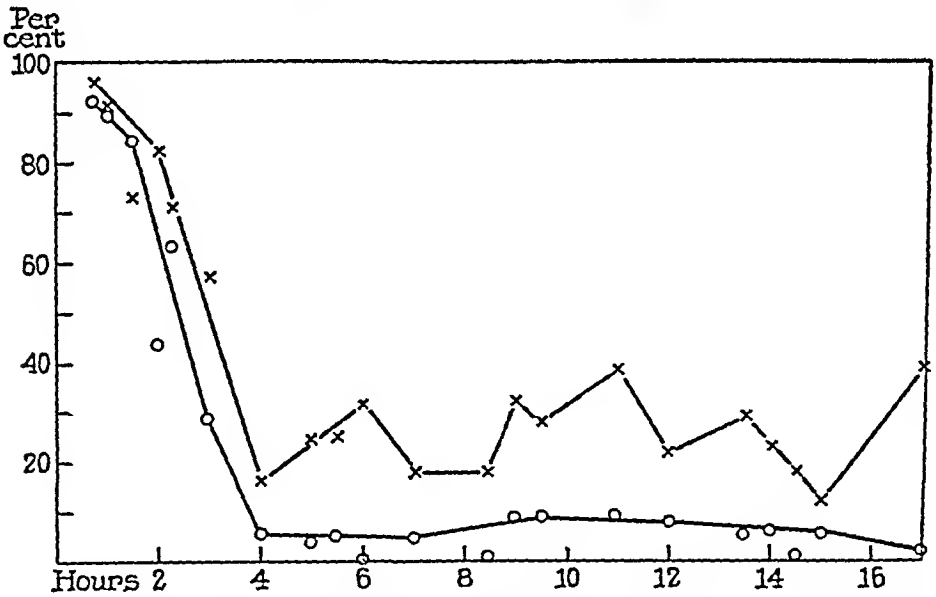


FIG. 1. Percentage of free (unphagocytized) tubercle bacilli in the exudate of mice during the first seventeen hours after inoculation of tubercle bacilli.  
O—O: H37 Ra (avirulent); X—X: H37 Rv (virulent).

tubercle bacilli, the percentage of leukocytes containing one or two micro-organisms increases with time. In contrast, the relative number of leukocytes containing a larger number of bacilli, ten and more, rapidly decreases during

the period of observation. In the case of the avirulent organisms the percentage of white cells containing many bacilli does not increase correspondingly but remains low throughout.

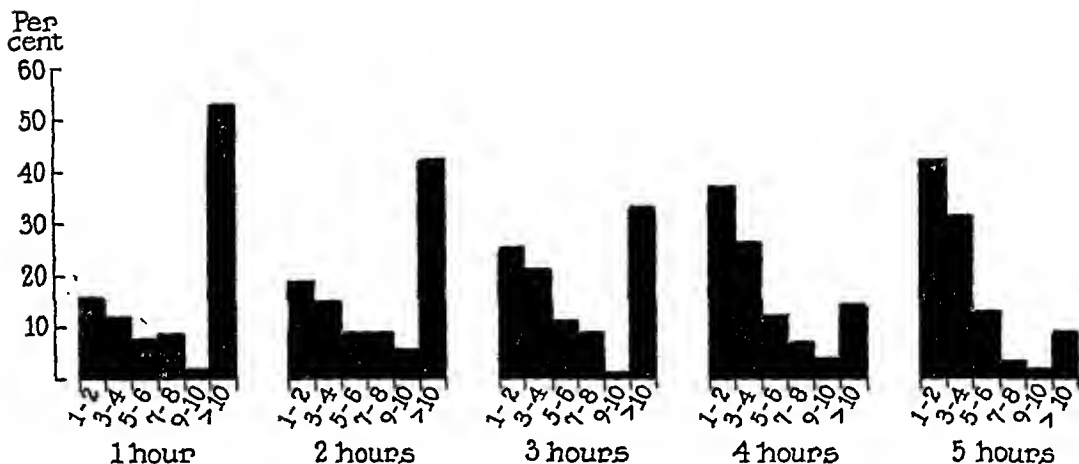


FIG. 2. Intracellular distribution of virulent tubercle bacilli (H37Rv) one to five hours after inoculation.

Each column represents the percentage of leukocytes in the exudate containing the number of tubercle bacilli indicated by the numerals on the abscissae.

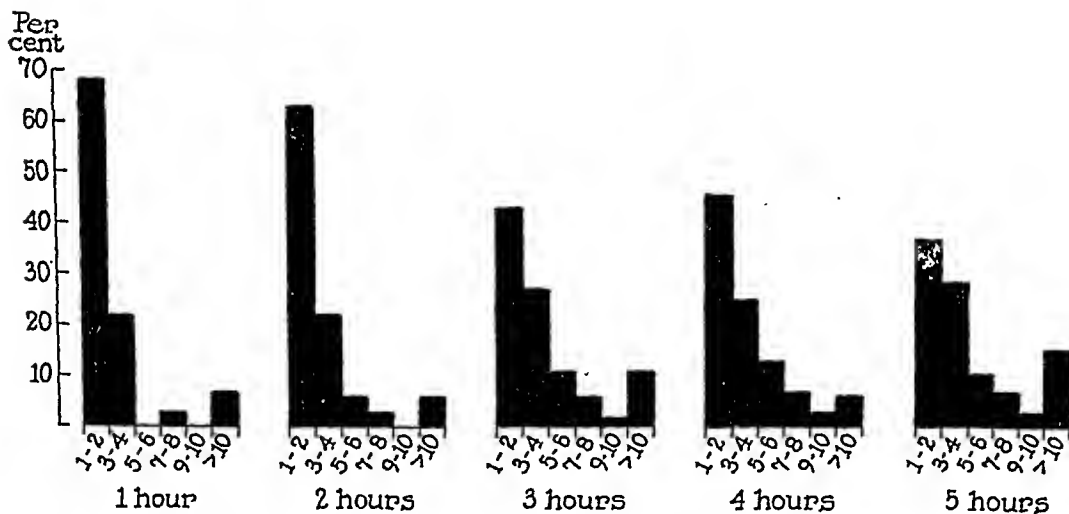


FIG. 3. Intracellular distribution of avirulent tubercle bacilli (H37Ra). Symbols as in figure 2.

*Experiments with avirulent bacilli grown in the presence of chick embryo extracts:* It has been shown in a preceding paper (2) that addition of chick embryo extracts to culture media alters the type of growth of the avirulent strain H37Ra of human tubercle bacilli, causing them to form "cords" similar to those produced by virulent strains. The behavior toward phagocytic cells of avirulent bacilli grown in the presence of chick embryo extract was determined by injecting bacilli under conditions similar to the ones used in the experiments recorded earlier in

the present paper. Care was taken in particular to use bacterial suspensions containing cell agglomerates no larger than those present in suspensions of H37Ra and H37Rv grown without embryo extract.

The results recorded in figure 4 illustrate that the distribution pattern in the phagocytic cells of H37Ra bacilli grown in presence of chick embryo extracts,

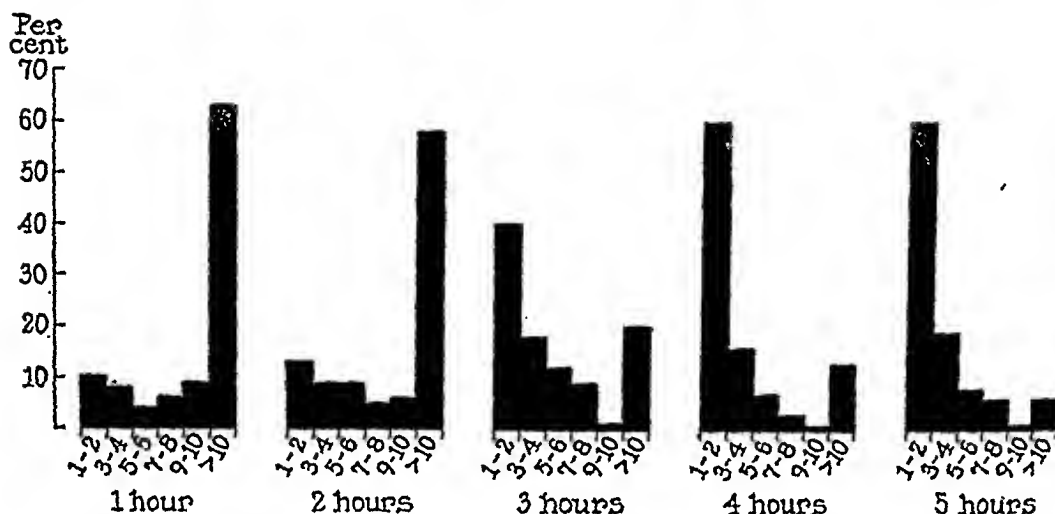


FIG. 4. Intracellular distribution of avirulent tubercle bacilli (H37Ra) grown in the presence of 0.5 per cent chick embryo extract. Symbols as in figure 2.

TABLE 2

*Per cent of leukocytes containing tubercle bacilli, and of free (unphagocyted) tubercle bacilli in the peritoneal exudate of mice injected with avirulent (H37Ra) and virulent (H37Rv) variants of tubercle bacilli*

| DAYS AFTER INJECTION | PER CENT OF                            |       |                                      |       |
|----------------------|--|-------|--------------------------------------|-------|
|                      | Leukocytes containing tubercle bacilli |       | Free (unphagocyted) tubercle bacilli |       |
|                      | H37Ra                                  | H37Rv | H37Ra                                | H37Rv |
| 1                    | 7                                      | 9     | 0                                    | 12    |
| 2                    | 8                                      | 12    | 1                                    | 20    |
| 4                    | 3                                      | 5     | 0                                    | 9     |
| 8                    | 2                                      | 5     | 0                                    | 26    |

although not identical with that presented by the virulent H37Rv, is very similar to it. Nevertheless, the rate of decrease of the numbers of phagocytic cells containing large numbers of bacilli is somewhat faster than in the case of the genuinely virulent strain.

*Observations during later stages of infection:* The phenomena thus far described occur within the first five hours following injection, at a time when the exudate consists chiefly of polymorphonuclear cells. When exudates are studied after more prolonged intervals of time, the main difference observed between virulent

and avirulent bacilli consists in a more complete disappearance of the latter. This is equally true for phagocytosed and for extracellular bacilli (table 2).

Preliminary observation has also been made of the effect of injecting bacillary suspensions into preformed exudates induced by injecting casein or 0.85 per cent saline twenty-four to forty-eight hours prior to the infection. These exudates contained larger numbers of mononuclear phagocytes. Only barely detectable differences in their behavior toward virulent and avirulent strains were observed.

#### DISCUSSION

The data presented in figure 1 and table 1 show that virulent and avirulent bacilli are phagocytosed at the same rate during the initial stage after intraperitoneal injection into white mice. The difference in effect of the two bacillary forms, however, is revealed by the fact that unphagocytosed bacilli were found throughout the whole period of observation in the exudate of animals infected with virulent bacilli but not in the case of the avirulent variants. In order to account for this observation, it is necessary to assume either that the virulent bacilli start multiplying outside the cells shortly after injection, or that they are constantly being released from the phagocytic cells which have engulfed them.

There are several reasons which favor the latter hypothesis. It is known that virulent tubercle bacilli grow in a characteristic parallel arrangement forming serpentine cords not only in culture media, but also in tissue cultures and in the peritoneal exudate of guinea pigs (11, 13, 21). In the present experiments such a parallel arrangement was not observed in the case of the extracellular bacilli during the first hours after injection. Indeed, the small cords which had been injected rapidly disappeared from the exudate. The bacillary cords were engulfed by the leukocytes and could be detected within the cells for a short time following phagocytosis. Then the white cells containing these bacillary cords disappeared from the preparation, leaving poorly stained shadows of cellular protoplasm in which the bacilli had increased in number. At that time the bacilli were no longer arranged in cords but were found to lie helter-skelter within the protoplasmic mass. Thus it appears that the bacillary cords are disrupted as a result of phagocytosis and that more or less simultaneously the leukocytes undergo lysis and release the bacilli as isolated organisms into the exudate. It is only in the later stages of infection, after four to five days, that cords can again be seen in the exudate. This corresponds to an observation made by Woodruff in guinea pigs (21), and the bacillary cords may represent organisms which have grown in the extracellular fluid.

The findings concerning the quantitative intracellular distribution of the virulent bacilli are in agreement with this hypothesis. It was observed that the high initial percentage of cells containing a large number of bacilli decreases rapidly, apparently in consequence of the lysis of these leukocytes. The increase in percentage of leukocytes containing only one or two bacilli might result from the fact that the breakdown of the bacillary cords would release isolated bacilli now available for phagocytosis as single cells.

The fate of the avirulent bacilli is in striking contrast to this situation. The

proportion of phagocytic cells containing large numbers of bacilli never was high, probably because these phagocytes, uninjured by their content, disappeared from the exudate and became fixed to the omental surface or found their way into the lymphatic channels. It is possible that the decrease in the percentage of cells containing only one or two avirulent bacilli, as contrasted with a relatively constant number of leukocytes with larger numbers of micro-organisms, resulted from the fact that leukocytes are not damaged by the bacteria which they have taken up and can engulf more of them before they are removed from the exudate.

Finally, the behavior of the avirulent bacilli grown in the presence of chick embryo extracts can be interpreted by assuming that, like the virulent forms, they exhibit a certain degree of toxicity for the white cells. Although not able to establish a progressive disease, these bacilli have been shown to possess some of the properties of the virulent strain (2).

The reactions which have been described occur at a comparatively slow rate and their significance will become apparent only when parallel observations are made with the simultaneous use of virulent and avirulent strains. Although the conditions used in the present study do not occur under natural circumstances, it is possible that similar phenomena occur when polymorphonuclear leukocytes meet the invading organisms in the natural disease. It seems also worth mentioning in this respect that the lytic breakdown of the leukocytes may result in the liberation of products, sphingomyelin, for example, which facilitate the further proliferation of tubercle bacilli (3).

It should be emphasized that polymorphonuclear leukocytes are predominant only during early stage of the inflammatory process, and that the mononuclear leukocytes which dominate the field after the initial period are also able to engulf the tubercle bacilli and probably to destroy them (6, 9). Nevertheless, the occurrence of extracellular organisms, even at the stage of monocytic predominance, suggests the possibility that virulent tubercle bacilli can exert some toxic effect on the monocytes as well as on the polymorphonuclear cells. In the course of tuberculous infection, the phagocytic power of the monocytes varies according to the level of allergy (10), and their ability to destroy bacilli is subject to simultaneous variation. The resistance of the monocyte toward the tubercle bacillus may not therefore be an absolute one, especially in the nonimmune animal.

#### SUMMARY

A study has been made of the comparative effects on phagocytic cells in the peritoneal exudate of mice of a virulent culture (H37Rv) and an avirulent variant (H37Ra) of the same strain of human tubercle bacilli.

Both virulent and avirulent bacilli were taken up at the same rate by polymorphonuclear cells during the initial stage of the infection.

Extracellular bacilli could still be seen several hours after injection, however, in the peritoneal exudate of animals which received the virulent bacilli, whereas avirulent bacilli could be found only in the intracellular phase.

The observed facts suggest that the virulent bacilli (but not the avirulent variants) can exert on the polymorphonuclear cells which have phagocytized them a lytic effect which results in the release of the bacilli into the extracellular fluid.

## SUMARIO

*La Relación entre Fagocitos y Bacilos Tuberculosos Humanos*

Este estudio versa sobre el efecto comparado de un cultivo virulento (H37Rv) y una variante avirulenta (H37Ra) de la misma cepa de bacilos tuberculosos humanos sobre los fagocitos en el exudado peritoneal de los ratones.

Durante el período inicial de la infección tanto los bacilos virulentos como los avirulentos fueron ingeridos en proporción igual por los polimorfonucleares.

Sin embargo, varias horas después de la inyección, todavía podían observarse bacilos extracelulares en el exudado peritoneal de los animales que recibieron los bacilos virulentos, en tanto que los avirulentos sólo se podían hallar en la fase intracelular.

Los hechos observados indican que los bacilos virulentos (pero no las variantes avirulentas) pueden ejercer sobre los polimorfonucleares que los han fagocitado un efecto lítico que da por resultado la liberación de los bacilos al líquido extracelular.

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# THE EFFECT OF IRON ON EXPERIMENTAL TUBERCULOSIS<sup>1,2</sup>

ROBERT G. BLOCH, GEORGE GOMORI,  
AND MARJORIE SPERRY-BRAUDE

## INTRODUCTION

Experiments in the chemotherapy of tuberculosis suggested the use of chemicals which could carry chemotherapeutic agents into the avascular caseous tuberculous areas. As these necrotic lesions are the chief harbors of tubercle bacilli and hence are the chief sources of distribution of new disease, the chemical attack against them is of the utmost importance.

In a series of publications, V. Menkin (1, 2, 3, 4, 5) reported the penetration of iron into caseous centers of tuberculous areas in rabbits when injected intravenously in the form of a 0.25 per cent solution of ferric chloride. The presence of iron in the tuberculous organs was demonstrated by the Prussian blue stain. Menkin also observed an inhibitory effect of iron on the development of experimental tuberculosis.

## EXPERIMENTAL

On the basis of Menkin's observations, the following experiments were carried out: Tuberculous infection in 20 rabbits was produced by subcutaneous inoculation in the groin of 1 mg. of bovine bacilli (Ravenel strain). The animals were divided into four groups and treated in the following manner:

Group I (4 rabbits) received intravenous injections of ferric ammonium citrate U. S. P.

Group II (4 rabbits) received subcutaneous injections of streptomycin.

Group III (6 rabbits) received intravenous injections of ferric ammonium citrate plus subcutaneous injections of streptomycin.

Group IV (6 rabbits) served as controls.

The injections of both iron and streptomycin were begun fourteen days after inoculation. Through the use of iron in the citrated form venous thrombosis was avoided and the injection of the chemical in much higher concentrations than those used by Menkin was possible.

The 10 animals in Groups I and III were treated with the iron compound on the following schedule:

The total amount of iron received by each animal was 790 mg. This is about two and a half times the largest dose given by Menkin to one of his rabbits (318 mg.) and almost seven times the average dose (114.5 mg.) which he administered in varying amounts to a total number of 67 rabbits in five of his experiments.

The schedule of streptomycin administration to the 10 rabbits in Groups II and III was as follows:

(a) first period of treatment, 50 mg. daily for ten days followed by a ten-day interval;

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<sup>2</sup> This study was aided by a grant from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service.

TABLE 1

*Findings of tuberculosis on macroscopic and microscopic examination*

| GROUP  | RABBIT<br>NUMBER | LUNG              | SPLEEN | LIVER | KIDNEY | LYMPH NODE |
|--|------------------|-------------------|--------|-------|--------|------------|
| I<br>Ferric ammonium citrate<br>(Killed 64th day)                        | 26               | ++                | 0      | 0     | 0      | +++        |
|  | 28               | ?                 | 0      | 0     | 0      | 0          |
|  | 48               | ++                | 0      | 0     | 0      | +++        |
|  | 49               | 0                 | 0      | ?     | 0      | 0          |
|  | (55)*            | Died of pneumonia |        |       |        |            |
| II<br>Streptomycin<br>(Killed 65th day)                                  | 31               | 0                 | 0      | 0     | 0      | ++         |
|  | 33               | 0                 | 0      | 0     | 0      | 0          |
|  | 36               | +                 | 0      | 0     | 0      | 0          |
|  | 38               | 0                 | 0      | ?     | +++    | +++        |
| III<br>Ferric ammonium citrate<br>plus streptomycin<br>(Killed 66th day) | 2                | 0                 | 0      | 0     | 0      | +++        |
|  | 27               | 0                 | 0      | 0     | 0      | —          |
|  | 34               | 0                 | 0      | 0     | 0      | —          |
|  | 35               | 0                 | 0      | 0     | 0      | —          |
|  | 40               | 0                 | 0      | 0     | 0      | +++        |
|  | 44               | 0                 | 0      | 0     | —      | +++        |
|  | (62)*            |                   |        |       |        |            |
| IV<br>Controls<br>(Killed 63rd day)                                      | 16               | 0                 | 0      | 0     | 0      | 0          |
|  | 29               | +++               | 0      | +     | 0      | 0          |
|  | (60)*            |                   |        |       |        |            |
|  | 37               | ++++              | 0      | 0     | 0      | 0          |
|  | (53)*            |                   |        |       |        |            |
|  | 39               | 0                 | +      | +     | 0      | +++        |
|  | 41               | ++                | 0      | 0     | 0      | +++        |
|  | 43               | 0                 | 0      | 0     | 0      | 0          |

\* Day after inoculation on which animal died spontaneously.

(b) second period of treatment, 50 mg. daily for nine days followed by a ten-day interval; and

(c) third period of treatment, 75 mg. daily for seven days.

The total dose received by each rabbit was 1,475 mg.

| Day     | Amount | Per cent concentration |
|---------|--------|------------------------|
| 1       | 1 cc.  | 0.5                    |
| 2       | 2 cc.  | 0.5                    |
| 3 to 7  | 5 cc.  | 0.5                    |
| 8       | 5 cc.  | 1.0                    |
| 9 to 26 | 5 cc.  | 5.0                    |

The animals were killed after sixty-three to sixty-six days. Rabbits in which death occurred spontaneously are designated in table 1 by the number of days elapsed from inoculation to the time of death.

## COMMENT

The findings, although not wholly conclusive in this small number of animals indicate that streptomycin alone had a definite and as much an inhibitory effect

on the development of tuberculosis as the combination of streptomycin with injections of the iron compound. The treatment by the latter alone resulted in only slight inhibition, if any.

FIG. 1

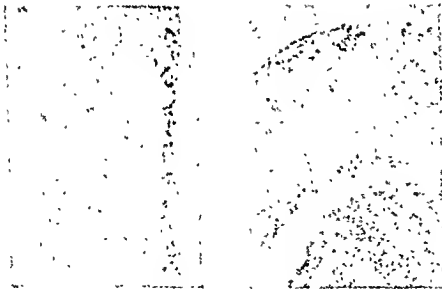


FIG. 2

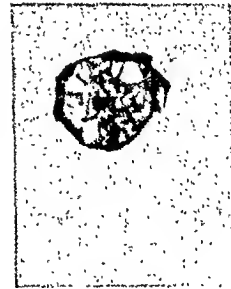


FIG. 3

FIG. 1. Surface view of the tuberculous lung of a rabbit. Prussian blue reaction. The intense surface staining of tubercles indicated by arrows.

FIG. 2. Section of lung shown in figure 1. The Prussian blue reaction was repeated on this slide to show iron deposits in the depth of tissues; only the pleural surface and superficial lymphatics stained.

FIG. 3: Section of tuberculous lymph node stained as in figure 2. The caseous central area remained free of iron.

The penetration of iron into the caseous centers of tuberculous lesions could not be verified by these experiments. Although the impregnations with Prussian blue resulted in similar surface staining of the tuberculous areas (figure 1) to that demonstrated by Menkin, it became apparent that the staining effect was confined to the pleural deposits of fibrin and to the superficial lymphatic elements, but failed to enter the caseous centers of tuberculous lesions (figure

2). Likewise, the caseous areas in tuberculous lymph nodes remained free of iron (figure 3).

#### SUMMARY

The results of these experiments on the penetration of caseous lesions by iron substantiate the findings of Steinmann (6), who was unable to verify Menkin's claims. Menkin (7) contended that the difference was due to Steinmann's use of a "totally different iron compound" and of the oral route of introducing the iron rather than by intravascular injection. This objection cannot be applied to the present experiments for, as in Menkin's, the iron was injected by the intravenous route only and a true iron salt was used. The behavior of ferric ammonium citrate is essentially the same as that of ferric chloride, except that in the former iron will probably circulate in the blood longer than in the latter, owing to the prevention of precipitation by citrate ions.

#### SUMARIO

##### *El Efecto del Hierro sobre la Tuberculosis Experimental*

Los resultados de estos experimentos referentes a la penetración de las lesiones caseosas por el hierro apoyan los hallazgos de Steinmann (6), quien no pudo comprobar los asertos de Menkin. Arguyó Menkin (7) que la diferencia se debía al empleo por Steinmann de un "compuesto férrico absolutamente distinto" y a la introducción oral del hierro más bien que por inyección intravascular. Este reparo no reza con los experimentos actuales, pues lo mismo que en los de Menkin, el hierro fué inyectado exclusivamente por vía endovenosa y se utilizó una verdadera sal férrica. El comportamiento del citrato férrico-amónico es esencialmente idéntico al del cloruro férrico, salvo que, con el primero, el hierro circulará probablemente más tiempo en la sangre que con el último, debido a impedirse la precipitación por yones de citrato.

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# THE PREVENTION OF PRIMARY TUBERCULOUS INFECTIONS IN MEDICAL STUDENTS<sup>1</sup>

The Autopsy as a Source of Primary Infection

GORDON M. MEADE<sup>2</sup>

## INTRODUCTION

The occurrence of several cases of clinical pulmonary tuberculosis in the student body of the University of Rochester School of Medicine and Dentistry prompted a study to determine, if possible, the sources of infection. One of the striking findings of this study was an indication that in this particular medical student body a chief source of primary infection was the autopsy. This paper will deal with those findings and the success achieved in reducing such infection by elimination of student contact with tuberculosis autopsy material.

## OBSERVATIONS

### *Methods of Preliminary Study*

From the beginning of the study (September 1937) Mantoux intradermal tests were performed with two strengths of PPD (0.00002 and 0.005 mg.). All students were tested initially on their entry to the school. On all those who did not react, the test was repeated every four months and, since March 1943, every three months, until a definite positive reaction was obtained, or until graduation if they remained negative. Equivocal reactions were regarded as negative and testing continued routinely until a definitely positive reaction was obtained, or throughout the period of the study. The minimal criterion for a positive reaction was the usual one of 5 mm. or more of induration. Erythema alone was considered a negative reaction.

### *Results of Preliminary Study*

In figure 1 may be seen the changes in percentage of positive reactors in each class during its four academic years. It was obvious when the first analysis of the tuberculin test results was made in early 1943 that the most striking increase in the percentage of positive reactors occurred during the second academic year. In figure 1 may also be seen the composite picture of the average annual percentage increases in the classes of 1938 through September 1944, inclusive. It should be noted that during the war years an academic year was nine months instead of twelve but the periods of exposure were unchanged in length as the length and content of the various curriculum courses were not altered.

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The average percentage of positive reactors on entry to school for these classes was 42.6. During the first year this percentage rose to 54.2 by its close. By the end of the second year the average percentage of those who reacted positively rose to 92. Thereafter there were slight increases to 96.6 at the end of the third year, and 97.1 at the end of the fourth year. The same data are treated in a different fashion in figure 2 which contains the percentage of all those students originally negative on entry to the school who became positive during each school year. Again the preponderance of increase in the second year is evident.

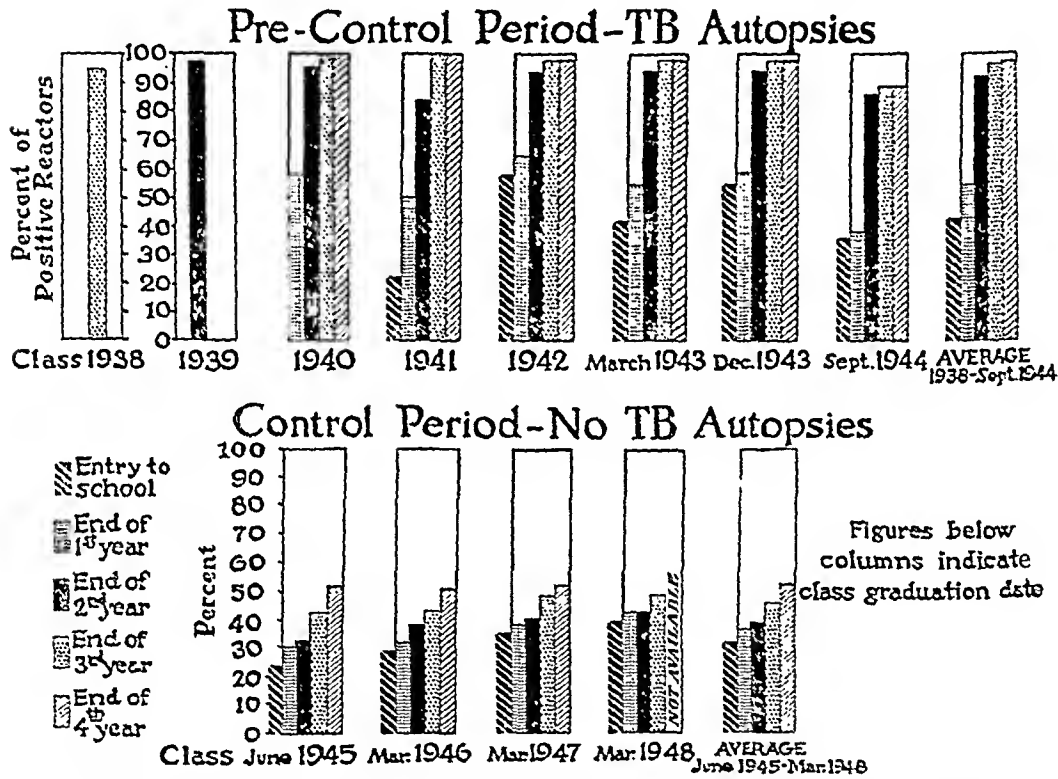


FIG. 1. Changes in percentage of positive tuberculin reacting students. Comparison of precontrol (tuberculosis autopsies) period classes with control (no tuberculosis autopsies) period classes.

Possible Sources of Second Year Primary Infection

Accepting the universal concept that conversion of tuberculin reaction from negative to positive indicates the occurrence of a primary tuberculous infection, it appeared from this analysis that somewhere in the second year there existed a significant source of primary infection. Therefore, it seemed pertinent to make the second year the first concentration point for a study of possible infection sources.

Within the school the most likely sources of infection during the second year were the courses in bacteriology, pathology and physical diagnosis. The first was fairly well eliminated from consideration because it was a routine

practice to use only heat-killed tubercle bacilli for class demonstrations; use of this material was closely supervised and was limited to two morning sessions. The course in physical diagnosis took place only during the last six weeks of the school year and subsequent to the period when detailed study showed that the great majority of the conversions had already occurred. Furthermore, cases of tuberculosis were very seldom used in teaching this subject.

The most probable source of infection, other than accidental, seemed to be the exposure of students to tuberculous tissues studied in the course in pathology.

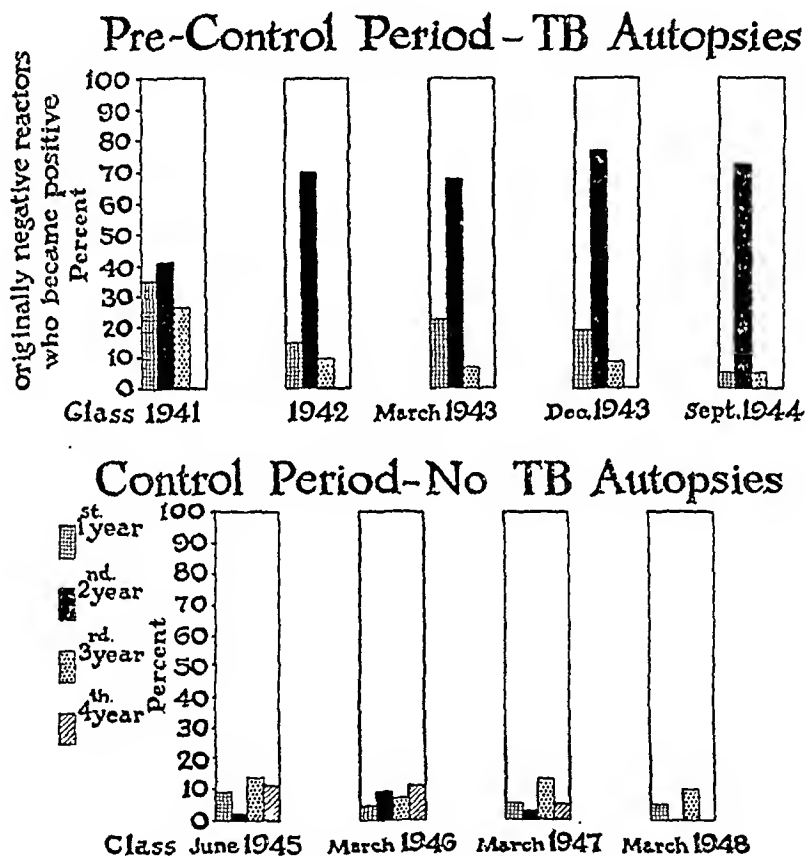


FIG. 2. Percentage of originally negative reacting students who became positive. Comparison of precontrol (tuberculosis autopsies) period classes with control (no tuberculosis autopsies) period classes.

The course ordinarily began the last week in November and continued through the first week in May, covering twenty weeks of study or exposure time. The marked increase in the percentage of positive reactors had taken place by February or March, some time before the end of the course in May.

During the course the classes of 40 to 60 students were divided into groups of four who were on call in rotation to participate in all autopsies. Students donned gown, apron and gloves but did not wear masks, and they actively assisted a department member in performing the autopsy. The student as-



sistants helped to remove, open, section, clean and examine all the organs. They were instructed on how to remove contaminated gloves and aprons but were not supervised after the initial instruction. In addition to assisting in autopsy performance, all students were given the opportunity once each week to handle and examine all tissues from the autopsies of the previous week, including those on tuberculous subjects. This material was unembalmed, refrigerated, and displayed in open pans about the autopsy room and students were encouraged to feel and examine the specimens closely. Thus, there was an opportunity for *all* students to have close contact with *all* the tuberculous material from autopsies performed during the course in pathology.

All autopsies for the local county tuberculosis sanatorium and the Strong Memorial and Rochester Municipal Hospitals were done by the Department of Pathology with medical students assisting. Those from the Strong Memorial and Rochester Municipal Hospitals included some on persons dying of tuberculosis. During the years covered by the study there were, on the average, 13 to 14 autopsies performed each year during the pathology course on tuberculous subjects with which students had opportunity for contact in the manner described.

### *Elimination of Tuberculosis Autopsies*

Admittedly the evidence for a relationship between the high second year tuberculin conversion rate and the contact with tuberculosis autopsy material was of an indirect nature. It seemed sufficiently striking, however, to warrant a trial period during which all such contact would be eliminated. Therefore, beginning in May 1943 with the class which graduated in June 1945, students were not allowed to participate in autopsies on known cases of tuberculosis. If an unsuspected case of tuberculosis was discovered at autopsy, they were excused from further participation. No tuberculous material was placed out for general examination and handling at the weekly fresh-tissue study periods. Instead the specimens were demonstrated by an instructor.

After this policy was adopted, there occurred a marked reduction in the number of tuberculin conversions among the students. Referring again to figure 1, it may be seen that the increase in the percentage of positive reactors in the second year was greatly reduced. Although some of the primary infections have been postponed to the third and fourth years, the final percentage of positive reactors is now only slightly more than half what it was previously.

It may be seen in figure 1 that in the classes affected by the new autopsy policy the positive reactor percentage at entry averaged 32.3; at the end of the second year it had risen only to an average of 38.8; and by graduation the average had reached only 51.9 as compared with 97.1 in the previous classes. In figure 2 may be seen the reduction in the percentage of originally negative reactors who converted during the second year which followed the change in policy.

As contact with autopsy room tuberculous material was the only factor eliminated or altered, it seems reasonable to conclude that the relationship to the lowered conversion rate is a real one.

Another expression of this relationship is presented in table 1. The number of tuberculosis autopsies, the number of tuberculin conversions and noneconversions occurring in second year students are compared for the two periods (i.e., the tuberculosis autopsy or precontrol period and the no tuberculosis autopsy or control period). The number of autopsies to which students were exposed in the ways previously mentioned was determined by careful examination of records and protocols of the Department of Pathology. The only autopsies included in the count were those in which students participated or had access to the material during the course, and in which there was open tuberculosis listed as a primary cause of death as proven by the postmortem findings.

In the precontrol period covered by the study there were 81 autopsies on tuberculous subjects. Of 139 students (in six classes) who were tuberculin negative at the start of the second year and were retested through the year, there were 112 who became tuberculin positive and 27 who remained negative. When students did not have close contact with autopsy material from tuber-

TABLE 1

*Comparison of number of tuberculosis autopsies, tuberculin conversions and nonconversions in second year students in precontrol and control periods*

|   | NUMBER OF<br>TUBERCULOSIS<br>AUTOPSIES | NUMBER OF<br>TUBERCULIN<br>CONVERSIONS | NUMBER OF<br>TUBERCULIN<br>NONCONVER-<br>SIONS | NUMBER OF<br>STUDENTS |
|---|--|--|--|-----------------------|
| Precontrol (tuberculosis autopsy) period (6 classes)..... | 81                                     | 112                                    | 27   | 139                   |
| Control (no tuberculosis autopsy) period (4 classes)..... | 0                                      | 6                                      | 150  | 156                   |
| Totals.....   | 81                                     | 118                                    | 177  | 295                   |

culous subjects (control period), out of 156 negative reactors (in four classes) only 6 converted and 150 remained negative.

The deviation of the observed number of conversions and noneconversions in the control period from the expected values (based on precontrol period values) is of overwhelming statistical significance.

#### DISCUSSION

The experience presented above is not without precedent. Hedvall (1) noted an excessive tuberculosis morbidity among medical students as compared with students in philosophy, theology and law, even though the percentage of negative reactors on entry was generally the same and the living conditions were equivalent. He found that medical students themselves had long suspected that the course in general pathology constituted a source of tuberculous infection. An investigation was made to determine during which course the originally tuberculin negative students became positive. In 16 of 47 cases of primary infection found during the study there was felt to be a significant connection

between the course in general pathology and the appearance of the primary infection. Thorough and repeated examinations of the autopsy rooms for the presence of tubercle bacilli disclosed that, in spite of all precautions as regards cleanliness during the postmortem examinations, tubercle bacilli were recoverable from the rooms and from different objects such as towels, trays, and dust on the autopsy tables, twenty-four hours after an autopsy on a tuberculous subject. As a result of these findings, Hedvall introduced more stringent precautions and limited necropsy examination of tuberculous patients by students as much as possible. The result during the first two years showed that for the first time all tuberculin negative reactors at the beginning of the course were also negative at its conclusion.

Morris (2) is convinced from her extensive experience with students at the Women's Medical College in Philadelphia that "At least one serious source of tuberculous infection for medical students lies in their participation in autopsy procedure on tuberculous cases and in attendance at prolonged sessions in the autopsy rooms."

The fairly frequent occurrence of tuberculomas of the skin in pathologists before the use of protective gloves is well known and attests to the reality of the autopsy as a source of infecting organisms.

Sloan (3) has shown that during routine examination of tuberculous lungs at autopsy, tubercle bacilli are projected for at least eight inches into the air from the tissues during slicing and handling. Sterile, clean glass plates were placed above the specimens during the examinations and tubercle bacilli were then recovered from them by culture.

The desirability of preventing primary infection of medical students with tubercle bacilli would seem to be unquestionable. It may be argued by some, however, that tuberculous infection in physicians is inevitable, that primary infections in young adults are innocuous and self-limited, and therefore preventive efforts are pointless. Such a viewpoint seems unsound on several counts.

First, while it is true that some of the students who succeed in graduating with negative tuberculin reactions may acquire infections later on in hospital residency or practice, it seems distinctly possible that the chances of this late infection, particularly after the hospital residency period, are definitely less than during the undergraduate period. Many will have little more contact with tuberculous persons than the lay individual, especially those who go into research, administrative fields and some types of practice. Studies on this point are desirable. Studies are now in progress on the students in this school who were tuberculin negative at graduation and who have remained for resident training in the Strong Memorial and Rochester Municipal Hospitals to determine what percentage become tuberculin positive during their services and when and where infection occurs. To date the group available for study is small but of 14 such individuals followed for periods up to three years there has been only one conversion. This occurred in a pathology intern who was negative to both strengths of PPD two weeks before graduation. Three weeks later he began service in pathology and two and one-half months subsequently he gave four plus reaction to second strength PPD. A chest roentgenogram ob-

tained one week later showed a soft exudative lesion in the left lung which did not respond to bed-rest, progressed and required pneumothorax therapy. On the basis of experiences of this sort, an attitude of acceptance of the certainty of primary infection without attempts at prevention seems indolent and defeatist.

Secondly, primary infections of natural origin are caused by an unknown dosage of tubercle bacilli of undetermined virulence and may lead to tuberculous disease, either immediately or later. Prevention of such uncontrolled infections will allow substitution in exposed individuals of a controlled type, as with BCG, without the risk of disease development and with the production of an increased resistance to virulent infections if they subsequently occur.

Third, the argument as presented by Myers, Diehl and Boynton (4) that primary infections in young adults are innocuous and self-limiting is by no means always true in the writer's experiences. A detailed report of these experiences is in preparation. Several investigators, such as Malmros and Hedvall (5), Frostad (6), Hedvall (7), and Malmros (8) agree that, while adult primary infections usually are nonprogressive and nonproductive of symptoms or roentgenographic changes, they not infrequently are "progressive and malignant." Malmros (8) states that the view is becoming more and more prevalent in Scandinavian countries that the majority of cases of pulmonary tuberculosis are a direct consequence of late primary infection. Pinner (9) recently gave a concise discussion of the importance of late primary infection in the development of progressive pulmonary tuberculosis. If in any way it is possible to avert the occurrence of even a very few such progressive, destructive lesions in young physicians, efforts to prevent primary infection are worthwhile. Furthermore, the possibility that, by eliminating a source of primary infection, a source of secondary infection may also be eliminated cannot be disregarded.

Even granting that but a very few of the primary infections have an unfavorable end result, it is callous and shortsighted to use this as an argument against attempting to prevent them. Unfortunately, there is no method available at the present time by which it is possible to determine at the onset which of these primary infections will progress and which will not, which require treatment and which do not. It is therefore necessary to render treatment to all of them, or at least to effect a marked modification of the patient's living regimen. As a result of labeling a student with the diagnosis of tuberculosis, there are powerful factors detrimental to his development which come into play, of which the roentgenogram alone gives no conception, whatever else it may disclose. It gives no measure of the lost time, the financial expense, the altered life plans, the frustrated ambitions, the deterioration of general physical status (and at times emotional), and the ever-present fear of relapse which result when a student develops this disease.

In this study it was possible to reduce markedly the number of primary infections by elimination of contact with tuberculous tissues. As will be reported elsewhere, there was also a striking concomitant reduction in the incidence rate of tuberculous disease.

It is not the intent of this report to maintain that all or the major number

of cases of medical student tuberculosis arise from primary infections acquired during courses in pathology. This study suggests, however, that at least in one school of medicine the autopsy room was an important source of primary infection and hence of tuberculous disease. It is suggested that other schools of medicine might profitably institute similar studies and practices.

#### SUMMARY

1. An intensive tuberculin testing program in a medical school with a high student tuberculin conversion rate and tuberculosis incidence rate revealed that the majority of primary infections (as evidenced by tuberculin reaction conversions to positive) were occurring during the second academic year.

2. Because contact with tuberculous tissues during the course in pathology seemed to be the most likely source of infection during the second year, all participation in tuberculosis autopsies and handling of tuberculous tissues by second year students were eliminated.

3. Prior to this change of policy the average percentage of positive reactors in each class at the end of the first year was 54.2; and by the end of the second year it was 92. Following this change of policy the average percentage of positive reactors in each class at the end of the first year was 36.4; by the end of the second year it was 38.8, and by the end of the fourth year it was only 51.9. A marked reduction in the number of primary infections during the second year had occurred.

4. The desirability of preventing primary tuberculous infections in medical students is stressed and the suggestion is made that other schools of medicine may find a like situation exists if similar investigations are made.

#### SUMARIO

##### *Prevención de las Infecciones Tuberculosas Primarias en los Estudiantes de Medicina*

1. Una intensa obra de comprobación con tuberculina en una facultad de medicina con elevados coeficientes de virajes en la reacción a la tuberculina y de incidencia de tuberculosis en los estudiantes reveló que la mayoría de las infecciones primarias (según denotaba el viraje de las reacciones tuberculínicas a positivas) ocurrían durante el segundo año académico.

2. Por parecer que el contacto con tejidos tuberculosos durante el curso en anatomía patológica era la causa más probable de infección durante el segundo año, eliminóse toda participación de los estudiantes de segundo año en las autopsias de tuberculosos y en la manipulación de tejidos tuberculosos.

3. Antes de este cambio de sistema, el porcentaje de reactores positivos en cada clase al terminar el primer año promediaba 54.2; y a fines del segundo año, 92. Después del cambio, el porcentaje de positivos en cada clase al terminar el primer año promedió 36.4; a fines del segundo año, 38.8, y al final del cuarto año, sólo 51.9. Durante el segundo año había ocurrido una decidida disminución en el número de infecciones primarias.

4. Recálcase la importancia de impedir las infecciones tuberculosas primarias en los estudiantes de medicina, e indícase que otras escuelas de medicina pueden descubrir situaciones parecidas si llevan a cabo investigaciones semejantes.

#### *Acknowledgment*

The author wishes to acknowledge with sincere appreciation the invaluable work of Dr. Einar Lic during the early part of this study.

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# TUBERCULOSIS AMONG PHILADELPHIA FOODHANDLERS<sup>1,2</sup>

KATHARINE R. BOUCOT<sup>3</sup> AND MARTIN J. SOKOLOFF<sup>4</sup>

## INTRODUCTION

Case-finding is the keystone in any adequate program for tuberculosis control with mass radiography a very effective technique for screening purposes. Surveys are being conducted on large population segments in industry, hospitals, schools, prisons, and on a community level. The administrative problems of roentgenography and reporting have been perfected, but total response of communities and adequate clinical follow-up remain problems.

Because annual physical examination is a requirement for licensure on some 43,000 Philadelphia foodhandlers, it was obvious that, were chest roentgenograms added to the medical requirements, a survey could be set up in which a 100 per cent response would automatically result. In addition, the study would be unique in that legal power would be available to ensure clinical follow-up on all significant cases.

## METHOD

On January 13, 1947, the Division of Tuberculosis of the Department of Health inaugurated a program of annual chest roentgenograms on all foodhandlers. A chest roentgenographic station was opened on that date. The basic Act of Assembly, approved by the Pennsylvania State Legislature on May 23, 1945, defines a foodhandler as an employee of any kind in a public eating or drinking place who, in any manner whatever, handles or comes in contact with any food or drink served to or provided for the public, and the proprietor or any member of the proprietor's family who handles said food or drink. Thus, the definition is extremely broad. All physicians registered to examine foodhandlers were notified that, following completion of their examination, it would be their duty to instruct the foodhandlers to present themselves to the foodhandlers' roentgenographic station where a photofluorogram would be taken without charge. No foodhandler's certificate is valid unless the date of the chest roentgenogram is officially marked thereon.

The 70 mm. photofluorograms are read daily by a certified radiologist. The United States Public Health Service classification is used in interpretation of the films. As the primary purpose of these surveys is the detection of infectious tuberculosis, all shadows are interpreted as tuberculous which could conceivably be tuberculous. According to this philosophy, a significant number of films read as tuberculous are ultimately proved to be nontuberculous, but it is unusual

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to find that a photofluorogram read as nontuberculous must be shifted to the tuberculous category. As the whole follow-up program centers on the cases with a survey reading of tuberculosis, it is believed that the technique maintains the most adequate tuberculosis control.

Briefly, the program calls for the following:

(1) Interview by a public health nurse of all cases interpreted as tuberculous except those interpreted as "minimal, probably inactive"; (2) a repeat roentgenogram on 14 by 17 film of all cases designated as "suspect" tuberculosis; (3) a repeat roentgenogram on 14 by 17 film of all cases classified "minimal, probably inactive," together with a clinical report from the foodhandler's private physician or a chest clinic; (4) in all other cases interpreted as tuberculous, reports from private physicians or chest clinics must be supplied promptly on at least three consecutive seventy-two-hour sputum concentrates, on a 14 by 17 film, together with a summary of the history, physical findings, diagnosis, recommendations and date of return for further observation. If sputum is not available for study, at least one culture of gastric contents is required.

If the requirements are not met within the prescribed period of time, and the time varies with the classification and impression of activity, the foodhandler is severed from employment. An attempt is made to be understanding rather than arbitrary, but it is rigidly insisted that the standards be met.



1, 1947, complete follow-up studies are only available since that date. Therefore, the following data are based on 29,474 foodhandlers examined between

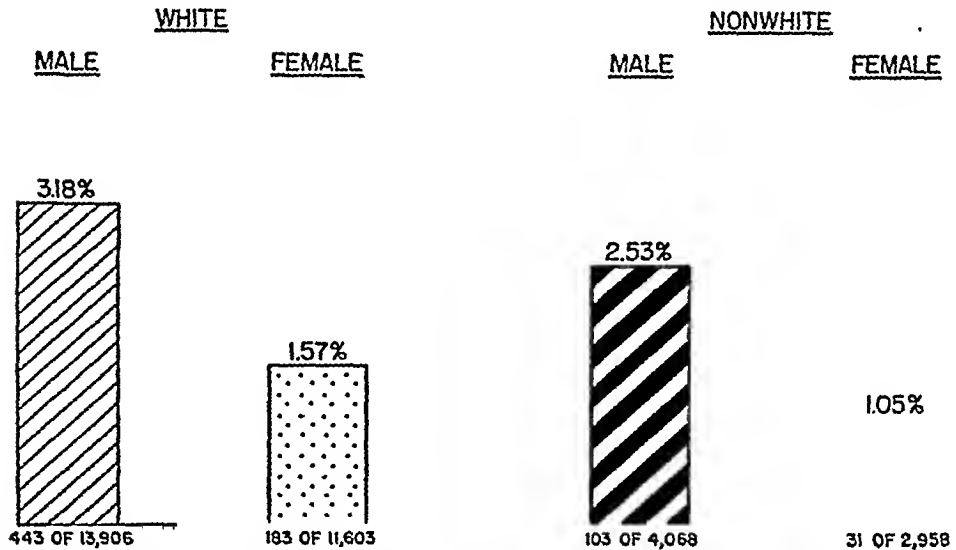


FIG. 1. Prevalence of tuberculosis among Philadelphia foodhandlers according to race and sex.

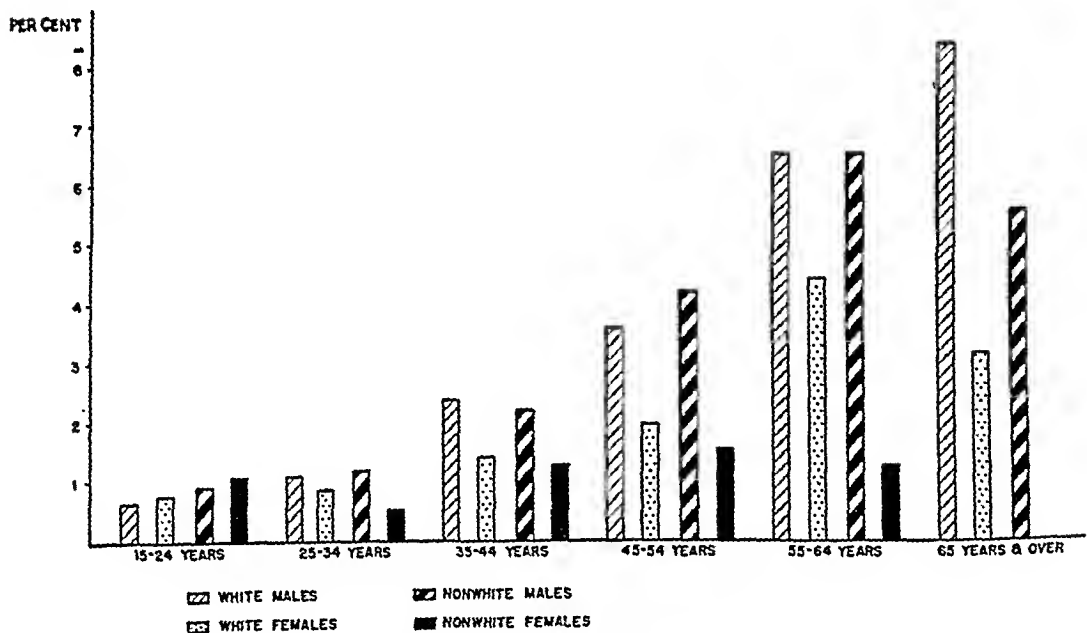


FIG. 2. Prevalence of tuberculosis among Philadelphia foodhandlers according to age, race and sex.

May 1, 1947, and January 31, 1948. Seven hundred and seventy-one (2.6 per cent) were classified as tuberculous or were shifted after further study to this category from the classification "suspect."

There were 587 (76.1 per cent) minimal cases, which is in keeping with the usual preponderance of minimal cases in surveys; 147 (19.1 per cent) moderately advanced; 20 (2.6 per cent) far advanced; and 17 (2.2 per cent) other tuberculous cases (figure 3).

The writers are aware of the fallacy of attempting to evaluate activity on the basis of a single film, but, for practical follow-up purposes, there is some virtue in estimating activity. There were 98 (0.3 per cent) films interpreted as "probably active." Figures 4 and 5 illustrate the type of film thus classified.

As of March 1, 1948, 66 cases have been hospitalized or have had hospitalization recommended. These represent 0.25 per cent of the total examined roentgenographically or 10 per cent of the patients on whom follow-up is avail-

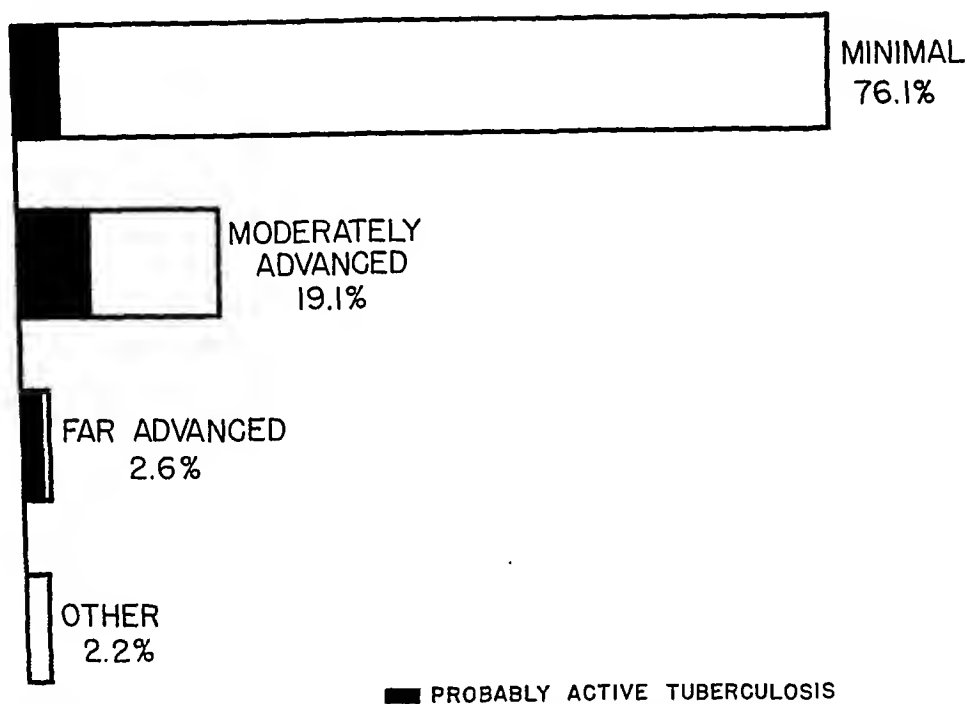


FIG. 3. Tuberculosis in Philadelphia foodhandlers according to stage and impression of activity.

able. These figures should be considered in the light of the brevity of follow-up. The longest period of follow-up is ten months while the shortest is thirty days. During this time, 43 foodhandlers have had sputum or gastric washings reported to be positive for tubercle bacilli.

There were 181 instances in which severance was resorted to in connection with the foodhandlers examined during the period of the study (figure 6). Only 0.6 per cent of Philadelphia foodhandlers required severance from employment. Of these, 68 were severed because of active tuberculosis. Of the 93 severed because they were uncooperative in obtaining required studies, 14 had survey roentgenograms interpreted as "probably active." These active cases were classified as 5 minimal, 7 moderately advanced, and 2 far advanced. None of

these probably active cases has returned for reinstatement, but one is known to have been hospitalized for tuberculosis. Only 35 of those severed because of lack of cooperation in obtaining subsequent studies have been reinstated. That is, one-third cooperated when it became evident that their jobs depended on their cooperation. Of the 20 who had been classified "suspect" on the miniature films and who failed to report as requested for a 14 by 17 retake, 7 subsequently

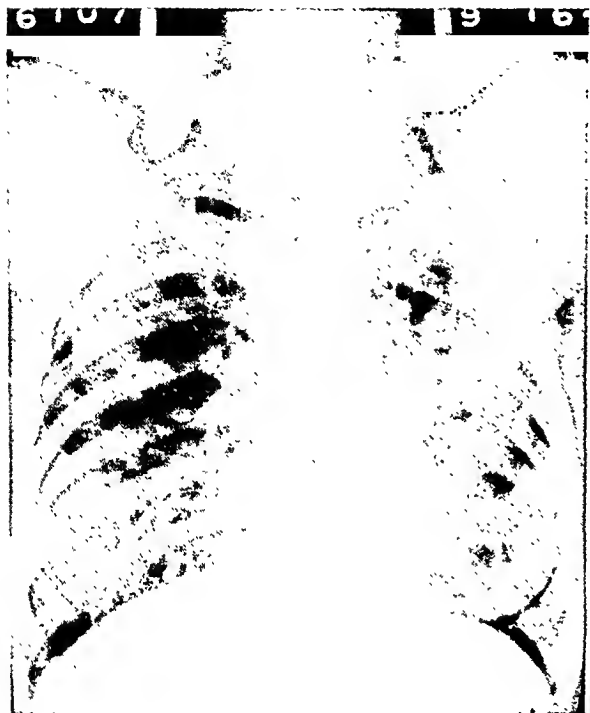


FIG. 4



FIG. 5

FIG. 4. (left) L. W., 23-year-old Negro woman dishwasher who had had cough for years productive of small amount of sputum daily. Pain in left chest for one month before survey film, September 16, 1947, which was read as far advanced, active. Sputum positive for tubercle bacilli and the patient was hospitalized October 4, 1947.

FIG. 5. (right) S. S., 41-year-old Negro dishwasher. One month prior to survey film had noted severe productive cough, exhaustion, fever and night sweats. Loss of 20 pounds over one month period. Survey film of September 5, 1947, revealed far advanced, active tuberculosis. Sputum positive for tubercle bacilli, patient hospitalized September 15, 1947, died of pulmonary tuberculosis December 13, 1947.

reported. Thus, on the whole, Philadelphia foodhandlers may be looked upon as a cooperative group. This cooperation is attributed in large measure to the excellence of the public health nurses to whom is entrusted the duty of personally interviewing each case interpreted as tuberculous. The interview conditions the whole subsequent attitude of these individuals.

It is of interest to compare the survey readings with the subsequent clinical diagnoses. In 147 of the 771 cases interpreted as tuberculous, no clinical diagno-

sis is yet available. This is a consequence of incomplete studies in 106 cases, to lack of cooperation in 40 instances, and to death from a cerebral accident in one case. In the 624 foodhandlers on whom follow-up reports are available, the survey impression of "tuberculosis" was confirmed in 473 instances, or 76 per cent. Sixty cases proved to be nontuberculous, 74 showed no abnormalities whatsoever and the balance are still diagnostic problems.

As far as survey impression of activity was concerned, 63 per cent of the cases interpreted as "probably inactive" were confirmed clinically as "inactive," 50 per cent of those believed to be "probably active" were deemed "active," while only 10 per cent of those designated "activity indeterminate" remained

|                          | NUMBER | PER CENT | NUMBER<br>REINSTATED |
|--------------------------|--------|----------|----------------------|
| Active tuberculosis..... | 68     | 0.2      | 3                    |
| Uncooperative            |        |          |                      |
| Inadequate study.....    | 93     | 0.3      | 35                   |
| 14 by 17 retakes.....    | 20     | 0.07     | 7                    |
| Total.....               | 181    | 0.6      | 45                   |

FIG. 6. Analysis of severances to March 1, 1948 of 29,492 foodhandlers X-rayed between May 1, 1947 and January 31, 1948.

|                        | ROUTINE         | CENTRAL COOPERATIVE CLINIC |
|------------------------|-----------------|----------------------------|
|                        | <i>per cent</i> | <i>per cent</i>            |
| Hospitalized.....      | 0.22            | 0.3                        |
| Positive sputum.....   | 0.15*           | 0.3†                       |
| Active clinically..... | 0.3             | 0.6                        |

\* Most of these are on smear alone.

† All proven by culture.

FIG. 7. Comparisons of significant tuberculosis in routine and in Central Cooperative Clinic follow-up.

in that category. It had been anticipated that careful clinical study would result in definition of the status of foodhandlers read as "activity indeterminate."

Clinical studies were conducted by 174 private physicians and 26 chest clinics. While the stated requirements outlined above were met, follow-up was not always ideal. Because annual chest roentgenograms are required, it should ultimately be possible to evaluate the clinical follow-up.

An interesting follow-up comparison is available in a survey of 2,622 foodhandlers employed by a large Philadelphia restaurant chain. This organization requested installation of a mobile unit at its headquarters. Arrangements were made for routine follow-up of all cases interpreted as tuberculous at the Central Cooperative Clinic. This is a research project sponsored jointly by the United States Public Health Service, the Division of Tuberculosis of the De-

partment of Public Health of Philadelphia, Temple Medical School and the Philadelphia Tuberculosis and Health Association. In the study the most meticulous methods available are used to follow approximately 500 survey cases interpreted as "probably tuberculous." Clinical studies include obtaining a 14 by 17 stereoscopic chest roentgenogram and a single postero-anterior film every three months, complete blood studies, physical examination, tuberculin and histoplasmin testing, sputum culture, repeated gastric washings cultures and special procedures such as bronchoscopy and the taking of lordotic films, planigrams, et cetera, when indicated. All patients return for study every three months. The project is to be continued for 5 to 10 years. It may be considered, therefore, that the 87 foodhandlers referred to in this research project are receiving ideal follow-up study without charge. Six have been uncooperative so no follow-up on them is available. Of the 81 individuals on whom a follow-up is available, 80 have had the survey diagnosis of tuberculosis confirmed. Eight patients, or 0.3 per cent of the entire group, have had sputum or gastric washing culture positive for tubercle bacilli. In five instances direct examination of these specimens had revealed no tubercle bacilli. Seven patients have been hospitalized and two of these have died of proved tuberculosis within six months of the survey. Significant clinical tuberculosis was found in 16 instances, which is 20 per cent of the cases designated as tuberculous on whom there have been follow-up studies and 0.6 per cent of the total group. The number of foodhandlers hospitalized was approximately the same in the group receiving routine follow-up and the group receiving Central Cooperative Clinic follow-up. Twice as many individuals, however, were found to have sputum or gastric contents positive for tubercle bacilli in the Central Cooperative group as in the routine group. In addition, every positive report was substantiated by cultural methods in the Central Cooperative Clinic group. Twice as many foodhandlers were found to have active clinical disease in the Central Cooperative Clinic as in the other group, which suggests that meticulous follow-up would give a higher yield of active tuberculosis than has been obtained in routine survey follow-up (figure 7).

#### DISCUSSION

Certain problems, most of which are common to all surveys, have presented themselves in the course of this emphasis on follow-up. For example:

There are inherent difficulties in evaluating activity in a given tuberculous lesion. What constitutes adequate study of an asymptomatic case discovered by survey?

What is the significance of a single direct sputum examination reported positive for tubercle bacilli? It is believed that confirmation of such a finding by culture should be required.

What is the magnitude of the public health menace represented by an individual with unchanging roentgenographic findings, no symptoms, but with an occasional specimen of sputum or gastric contents which is positive for culture? It is the present policy to recommend that such individuals seek employment

other than foodhandling, but there are some mental reservations as to the hazard they represent.

The writers have been impressed by the number of radiologists who have been willing on a single 14 by 17 film to give a definite report regarding the stability of a particular lesion. At the Central Cooperative Clinic, where stereoscopic 14 by 17 postero-anterior films are exposed, it has frequently been demonstrated that just by having the patient step aside and step back the change of position will cause the lesion to have a completely different appearance by roentgenogram or to disappear entirely behind a bony structure. Therefore, considerable effort has been expended in comparing films taken by clinicians with the survey films and in corresponding with these physicians in an effort to convince them of the impossibility of judging stability on any single film.

How can the clinician be educated to the public health importance of excluding tuberculosis in a given case? Certain ideas handed down from textbook to textbook persist in the minds of physicians. One of these is the extreme rarity of basal tuberculous lesions. Another is the notion that tuberculosis is a disease of young people. A third is the idea that active tuberculosis cannot be present without symptoms.

#### SUMMARY

1. The prevalence of tuberculosis among Philadelphia foodhandlers, as interpreted by roentgenographic survey technique was 2.3 per cent during the ten month period, April 1, 1947, to January 31, 1948. This is identical with the figure reported in 1946 for Philadelphia industrial workers.

2. Of 771 foodhandlers whose survey films were interpreted as tuberculous, subsequent clinical reports were available on 81 per cent after a period of follow-up varying from one to ten months. These reports confirmed the presence of tuberculosis in 76 per cent.

3. Annual roentgenographic chest examinations of Philadelphia foodhandlers has proved practicable. In the first nine months during which the perfected program has been in operation, it has resulted in the recommendation for hospitalization of 66 active cases of tuberculosis. This represents 0.25 per cent of the foodhandlers examined roentgenographically.

4. Because of Philadelphia's legal requirements for the issuance of licenses to public eating and drinking places, it is possible to follow chest lesions more carefully in the group of foodhandlers than in any other population segment.

5. Mass radiography is not merely a case-finding technique, but is a powerful method of education for both lay and professional groups.

#### SUMARIO

##### *Tuberculosis entre los Manipuladores de Alimentos*

1. A la luz de una encuesta radiográfica, la frecuencia de la tuberculosis entre los manipuladores de alimentos de Filadelfia representó 2.3 por ciento durante el período de diez meses, de abril 1, 1947 a enero 1, 1948. Esta cifra es idéntica a la comunicada en 1946 para los obreros de la ciudad.

2. De 771 manipuladores de alimentos cuyas radiografías fueron interpretadas como tuberculosas durante la encuesta, hubo después informes clínicos asequibles para 81 por ciento, tras un período de observación que varió de uno a diez meses. Estos informes confirmaron la presencia de tuberculosis en 76 por ciento.

3. Los exámenes radiográficos anuales del tórax de los manipuladores de alimentos de Filadelfia han resultado factibles. En los primeros nueve meses en que ha funcionado el sistema perfeccionado, ha hecho recomendar para hospitalización a 66 casos activos de tuberculosis, lo cual representa 0.25 por ciento de los manipuladores examinados radiográficamente.

4. Debido a las disposiciones que gobiernan en Filadelfia la expedición de permisos a los establecimientos públicos de comida y bebida, es posible observar las lesiones torácicas con más cuidado en el grupo de manipuladores de alimentos que en ningún otro segmento de la población.

5. La radiografía colectiva no es una mera técnica para el descubrimiento de casos, sino también un poderoso medio educativo para los grupos laico y profesional.

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# "MYCOBACTERIUM TUBERCULOSIS NO. 607" AND SIMILAR DOUBTFUL TUBERCLE BACILLI

A Review

WALTER C. TOBIE<sup>1</sup>

In 1932, Hastings and McCarter (9) called attention to the fact that the so-called *Mycobacterium tuberculosis* variety *hominis* No. 607 of the American Type Culture Collection does not have the characteristics of a true tubercle bacillus because of its nonpathogenicity and very rapid growth, including rapid growth on plain agar, a medium which does not ordinarily support the growth of tubercle bacilli. They also showed that the early history of this strain is very obscure, and that F. G. Novy (who was alleged to have brought it to the United States in 1888) actually acquired it from another source and always was in doubt about the strain, regarding it as being a saprophyte. They also showed that an alleged *bovis* strain, No. 599 of the American Type Culture Collection, had cultural characteristics very similar to those of No. 607. They therefore concluded that there was little or no reason for considering these two strains to be tubercle bacilli.

Reed (20) later pointed out that the criteria applied by Hastings and McCarter were too strict, as the criterion of nonpathogenicity would rule out the attenuated bovine Calmette and Guérin (BCG) strain as a tubercle bacillus. Nevertheless, most of the other objections raised by Hastings and McCarter remained unanswered.

The question of what constitutes a tubercle bacillus is fundamentally one of definition. It would seem reasonable to define the bacillus as one which is not markedly different in cultural characteristics from known pathogenic strains, and which either now or formerly is definitely known to have fulfilled Koch's postulates and to have produced typical lesions in appropriate experimental animals. This definition is broad enough to include organisms of known history such as the BCG strain, but narrow enough to exclude strains such as No. 607 and probably also No. 599.

Despite the doubts raised by Hastings and McCarter (whose paper seems to have been generally overlooked), publications have continued to appear in which No. 607 is called *Mycobacterium tuberculosis* (4, 6, 7, 10, 17, 18, 19, 23, 25) with little, if any, qualification. A number of other papers could also be cited in which No. 607 was apparently accepted as being a nonpathogenic, rapidly growing strain of human tubercle bacillus. In at least one case (21), No. 599 was accepted without apparent question as being an authentic bovine strain.

A few workers have dealt with No. 607 with greater reserve. Thus Youmans (27) refers to it merely as "National Type Culture Collection organism 607, an avirulent rapidly growing acid-fast bacillus." He found that No. 607 was

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inhibited by much lower concentrations (roughly one-tenth as much) of sulfanilamide, sulfathiazole, and sulfadiazine than the known virulent human strain H37Rv, and comments on the possible fallacy involved in using organisms such as No. 607 for *in vitro* tests of potential chemotherapeutic agents. In a recent paper on the action of penicillin on tubercle bacilli, Kirby and Dubos (13) mention that "No. 607, which is often used in studies of tubercle bacilli, does not fulfill the cultural and biological requirements of a true tubercle bacillus."

An older case in which either No. 607 or a very similar strain was used under a different designation, is in the series of ten papers by Kendall *et al.*, (11). Among the organisms used was "culture W" obtained from Professor Wherry of the University of Cincinnati. It was rapidly-growing and avirulent for guinea pigs, although allegedly originally a human tubercle bacillus, "a descendant of a culture from Koch's laboratory, brought to this country by Professor Vaughan of the University of Michigan." The other characteristics which Kendall and co-workers give for their "W" strain are very suggestive of No. 607. In the first paper of the series, the authors frankly admit that two of the cultures used "particularly W, in virtue of their avirulence for guinea pigs, might be questioned with respect to their authenticity as human tubercle bacilli."

The literature also contains many papers in which no serial numbers or other definite strain designations are applied to alleged tubercle bacilli, which are merely vaguely characterized as "nonpathogenic rapidly growing human strain," "rapidly growing avirulent strain," "avirulent Novy strain of tubercle bacilli," and the like. In many such cases, the organisms were undoubtedly No. 607 or something similar.

Gordon (now at the American Type Culture Collection) found among the acid-fast bacilli at Cornell University a culture labeled "Koch's original strain" which nevertheless had the cultural characteristics of *M. smegmatis*. She also reports that "the ATCC strains Nos. 599 and 607 also have the characteristics of *M. smegmatis*" (8). When the next edition of the American Type Culture Collection catalogue of cultures is issued, it is planned to indicate that Nos. 599 and 607 differ from fully authenticated strains of *M. tuberculosis* (8).

The work of Kelner and Morton (12) may also be interpreted to indicate that No. 607 resembles *M. smegmatis* more closely than it does *M. tuberculosis*. From an actinomycete, they isolated what they called an anti-smegmatis factor, since it showed its highest activity against a strain of *M. smegmatis* (University of Pennsylvania strain P-49). The factor had only a slight activity against *M. tuberculosis* variety *bovis* (Ravenel strain), but inhibited No. 607 at about the same high dilutions which were effective against their *M. smegmatis*.

Additional evidence that No. 607 differs markedly from ordinary tubercle bacilli is the fact that it is very insensitive to *p*-aminosalicylic acid (PAS), at present being tested in experimental tuberculous infections in animals (5, 15, 26, 28) as well as being subjected to clinical trials (1, 3, 14, 15, 24) and which is extremely specific in inhibiting the growth of true tubercle bacilli, both virulent and nonvirulent. Lehmann (14, 15) found that this compound inhibited the growth of the BCG strain at about 0.15 mg. per 100 cc. Strain H37Rv was

inhibited at the same concentration, but with No. 607 there was no inhibition at 150 mg. per 100 cc. (16). Sievers (22) found that 19 species (a total of 37 strains) of pathogenic and nonpathogenic bacteria (other than mycobacteria) were inhibited only by 1.25 to 2.50 per cent of PAS, while 4 strains of human tubercle bacilli were inhibited at the same levels as reported by Lehmann.

In a modified Kirchner medium containing Tween 80 and albumin (similar to the medium used by Dubos (2)), White (26) found that the resulting diffuse sub-surface growth of No. 607 was not inhibited by 128 mg. of PAS per 100 cc. of medium. On the other hand, the virulent human strain H37Rv and the avirulent human strains H37Ra, R1Ra, H4Ra, and JH16Ra, as well as the virulent bovine strain D4 and the avirulent BCG, were inhibited by 0.25 mg. of PAS per 100 cc. or even considerably less.

Youmans and associates (28) reported that one bovine and 17 human strains of tubercle bacilli (some of which were resistant to streptomycin) were inhibited by concentrations of 0.08 mg. of PAS per 100 cc. or even less, while one avian strain was inhibited by 0.625 mg. per 100 cc. On the other hand, No. 607 was highly resistant to PAS, growth occurring even at concentrations of 100 mg. per 100 cc.

#### SUMMARY

A large amount of evidence has now accumulated indicating that culture No. 607 of the American Type Culture Collection differs markedly from true tubercle bacilli and has a strong resemblance to *M. smegmatis*. Culture No. 599 also resembles *M. smegmatis*. Accordingly, it seems desirable that these strains (and similar rapidly growing avirulent strains) should no longer be called *M. tuberculosis*. Experimental work with such strains under this name tends to confuse rather than to clarify knowledge of the true tubercle bacilli. It is theoretically conceivable that in the course of repeated subculturing a tubercle bacillus might not only lose its pathogenicity but might also acquire the ability to grow rapidly on media which do not ordinarily support tubercle bacilli. The burden of proof rests upon the users of such strains, however, and in a great majority of cases such organisms at present in experimental use are probably only misnamed saprophytes.

#### SUMARIO

*El "Mycobacterium Tuberculosis No. 607" y los Bacilos Tuberculosos Dudosos Semejantes*

Un caudal de datos ya acopiados indica que el cultivo No. 607 de la Colección Americana de Cultivos Tipos discrepa notablemente de los verdaderos bacilos tuberculosos, guardando una poderosa semejanza al *M. smegmatis*. El Cultivo No. 599 también se parece al *smegmatis*. Parece, pues, conveniente que dichas cepas (y cepas avirulentas semejantes de rápido desarrollo) no sean ya más denominadas *M. tuberculosis*. La experimentación llevada a cabo con dichas cepas bajo tal nombre enreada más bien que esclarece nuestros conocimientos de los verdaderos bacilos tuberculosos. Teóricamente, es concebible que, en el

transcurso de repetidos subcultivos, un bacilo tuberculoso puede no tan sólo perder su patogenicidad sino también adquirir la capacidad para desarrollarse rápidamente en medios que no suelen sostener bacilos tuberculosis. Sin embargo, la prueba dicho fenómeno corresponde a los que emplean tales bacilos, siendo lo más probable que en la gran mayoría de los casos los microbios de ese género usados actualmente para experimentación no sean más que saprofitos bautizados erróneamente.

#### Acknowledgment

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## LETTERS TO THE EDITORS

### CYTOCHEMICAL REACTION OF VIRULENT TUBERCLE BACILLI

October 7, 1948

*To the Editors of the American Review of Tuberculosis:*

Our attempts to identify the cellular structures of tubercle bacilli which enable them to multiply in animal tissues have led us to recognize a cytochemical property of the bacterial cells which appears to be correlated with virulence. This correlation has been established by comparing the behavior toward the cytochemical test of cultures of human, bovine, and avian bacilli of various degrees of virulence.

Cultures of virulent tubercle bacilli are known to give rise to variant forms which are incapable of producing progressive disease in experimental animals; for example, the variant culture, H37Ra, derived from the virulent human strain, H37Rv, cannot establish infection either in guinea pigs (Steenken, W., Jr., and Gardner, L. U., *Am. Rev. Tuberc.*, 1946, 54, 62) or in mice (Pierce, C., Dubos, R. J., and Middlebrook, G., *J. Exper. Med.*, 1947, 86, 159). All attempts to differentiate qualitatively between these two variant forms by immunological reactions have so far failed. On the other hand, it has been recognized that there exist constant and striking morphological differences between the pattern of growth of virulent and avirulent cultures of mammalian tubercle bacilli. In the virulent forms, the cells have a tendency to orient themselves in parallel in the direction of their long axis, often adhering to each other to give long serpentine "cords"; the markedly attenuated forms, on the contrary, grow in a nonoriented manner (Middlebrook, G., Dubos, R. J., and Pierce, C., *J. Exper. Med.*, 1947, 86, 175).

The cytochemical test which differentiates these two forms is carried out as follows:

The washed bacterial cells are resuspended in an aqueous solution of 5 per cent sodium chloride and 1 per cent sodium barbiturate (or other adequate alkaline buffer). To this alkaline suspension is then added a small amount of aqueous solution of the basic dye, neutral red, and the system is observed at room temperature.

Because of the alkalinity of the medium, the solution of dye immediately becomes yellow. However, within a few minutes after exposure to the dye, the cells of H37Rv (virulent) begin to bind it and this binding is associated with a change of the dye from yellow to purple red. The process usually runs to completion within thirty minutes. At that time, the dye remaining in solution is yellow, whereas that fixed on or in the cells is bright red, despite the extreme alkalinity of the medium. In the case of H37Ra (avirulent), no significant fixation of the dye occurs and the cells are colored yellow like the soluble medium.

The amount of dye fixed by H37Rv is of the order of 1 per cent of the dry weight of the cells. If the concentration of the dye used in the test is such that the ratio of weight of cells to weight of dye is too small, all the dye is fixed by the cells in the red state and the supernate becomes colorless.

Many unrelated substances can mask the reaction, in particular, various components of bacteriological media. For this reason it is essential that for optimum results the test be carried out with cells washed free of these masking substances. We have found, in practice, that the best results are obtained with cells previously treated by two consecutive washings with 50 per cent methanol, the cells being maintained each time for one hour at 37° C. in the solvent before being separated by centrifugation.

There is not as yet sufficient chemical information available to warrant an interpretation of the observed facts. Nevertheless the study of 22 human and bovine strains of tubercle bacilli, including attenuated BCG strains, seems to justify the conclusion that the ability to bind neutral red in the form of its anion is characteristic of those cultures which exhibit to a greater or lesser degree the serpentine pattern of growth.

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## SEROLOGIC REACTION IN TUBERCULOSIS

October 7, 1948

*To the Editors of the American Review of Tuberculosis:*

While investigating antigenic components of tubercle bacilli and their reactions with the sera of experimental animals, we have observed that a water-soluble component of extracts of tubercle bacilli and of Old Tuberculin preparations can be firmly adsorbed onto sheep red blood corpuscles. Red cells treated in this way, we have found, are agglutinated by sera from rabbits previously injected with tubercle bacilli and by the sera of patients with active tuberculosis. Detailed description and analysis of this phenomenon will be presented in a forthcoming issue of the *Journal of Experimental Medicine*.

The technique of preparing the reagents and performing this test may be briefly described as follows. An appropriate volume of washed, packed sheep red cells is added to an excess of isotonic, neutral, dialyzed solution of a crude polysaccharide fraction of tubercle bacilli such as can be prepared by extracting the bacilli with aqueous dibasic phosphate solution after exhaustive extraction with 88 per cent phenol solution. The red cells are incubated in suspension with this extract and thereby adsorb the polysaccharide material. (Very small amounts of such material will sensitize sheep erythrocytes.) Then, the red cells are washed with isotonic saline to remove any material not firmly adsorbed onto them. Finally, they are suspended in 0.5 per cent concentration in saline and used as agglutinin in the hemagglutination test.

The serum to be tested is first heated to inactivate complement and then treated twice, each time with approximately one-fifth of its volume of washed, packed, unsensitized sheep red cells, in order to remove any antibodies which might agglutinate the untreated cells.

The hemagglutination test is performed by adding to dilutions (1:8 to 1:1024) of absorbed serum an equal volume of 0.5 per cent suspension of the sensitized red cells. Appropriate controls consisting of unsensitized red cells in the lowest dilution of serum and of sensitized red cells in saline, or in a serum known to be negative, are included in each test.

The possibility that clinical application of this test may be of value as an aid in the diagnosis of tuberculosis, as well as in following the serum antibody titre against specific components of the tubercle bacillus during the course of therapy, prompts us to write this letter.

We possess no information as to the bearing of the test upon resistance to the disease, or as to its significance as a measure of "activity" of the infection. We should like to point out, however, that its high degree of sensitivity, its reproducibility and its ease of performance give it some advantage over other types of serological reactions which have been available in the past for the detection and measurement of antibodies in human beings against polysaccharide components of the tubercle bacillus. Furthermore, at least two characteristics of this test are of clinical interest: (1) no false positive reactions have been observed with sera yielding positive reactions for syphilis; and (2) the sera of healthy individuals with high skin sensitivity to tuberculin (and without evidence of clinical tuberculosis) fail to agglutinate the specifically sensitized red cells.

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## AMERICAN TRUDEAU SOCIETY

### Postgraduate Courses in Pulmonary Diseases

The following postgraduate courses in pulmonary diseases are scheduled for the first half of 1949 by the American Trudeau Society, Medical Section of the National Tuberculosis Association. This program is conducted under the auspices of eight regional committees, covering all states, and the provinces of Canada, in cooperation with the medical schools of leading universities.

Applications may be obtained from the American Trudeau Society, 1790 Broadway, New York 19, New York. These courses are generally oversubscribed and physicians interested in applying are urged to request application forms as early as possible.

By special arrangement with the Department of Medicine and Surgery of the Veterans Administration, physicians employed by that agency are invited to participate. The request for detail to these courses originates in the branch and regional offices of the Veterans Administration and duplicate applications are required.

Physicians applying under Public Law 346, (G I Bill) should so state when filing applications with the Society.

January 24-29, 1949  
Los Angeles, California

Region VII comprising the states of: Washington, Oregon, California, Idaho, and Nevada; and the provinces of Alberta and British Columbia, Canada. This one week course will be held in cooperation with the College of Medical Evangelists, the University of Southern California School of Medicine, and the University of California at Los Angeles Medical School.

Tuition—\$50.00

March 7-12, 1949  
Indianapolis, Indiana

Region V comprising the states of: Ohio, Indiana, Michigan, Illinois, Wisconsin, Missouri, Iowa and Minnesota; and the provinces of Manitoba and Saskatchewan, Canada. This one week course will be held in cooperation with Indiana University School of Medicine.

Tuition—\$50.00

March 13-26, 1949  
New Orleans, Louisiana

Region IV comprising the states of: Alabama, Arkansas, Louisiana, Mississippi, Oklahoma and Texas. This two week course will be held in cooperation with Tulane University of Louisiana School of Medicine and Louisiana State University.

Tuition—\$100.00

April 4-9, 1949  
Atlanta, Georgia

Region III comprising the states of: Maryland, Virginia, West Virginia, Kentucky, Tennessee, North Carolina, South Carolina, Georgia, Florida and the District of Columbia. This one week course will be held in cooperation with Emory University School of Medicine.

Tuition—\$50.00

July-August, 1949  
Denver, Colorado

Region VI comprising the states of: Colorado, North Dakota, South Dakota, Nebraska, Kansas, New Mexico, Arizona, Utah, Wyoming and Montana. This two week course will be held in cooperation with the University of Colorado School of Medicine.

Tuition—\$100.00



Spring or  
Summer, 1949

Region VIII is planning a course at Saranac Lake, N. Y., chiefly for physicians from Northern New York and the Canadian Province of Quebec. This will be held in cooperation with medical schools of the area and The Trudeau Sanatorium. The dates have not yet been announced but information will be sent to those requesting it when available.

Special attention is directed to the following course for general practitioners which is being given in cooperation with The St. Louis University School of Medicine, January 17, 18, 19, 1949. Applications for this course should be obtained from the Executive Secretary of the Missouri Trudeau Society, 411 North 10th Street, Room 505, St. Louis 1, Missouri.

This is the second course for general practitioners included in the American Trudeau Society's program of postgraduate opportunities. There follows a summary of some of the subjects to be presented by leaders in the field of pulmonary disease:

**Symptomatology in Chronic Pulmonary Disease**—Practical evaluation of cough, pain, hemoptysis and dyspnea. Julius L. Wilson, M.D., Professor of Clinical Medicine, Tulane University School of Medicine; Head of Section on Chest Diseases, Ochsner Clinic, New Orleans, La.

**Physical Examination of the Chest**—its limitations. Paul Murphy, M.D., Assistant Professor of Clinical Medicine, St. Louis University School of Medicine, St. Louis, Mo. **Chest Films**—how to obtain satisfactory ones. Don C. Weir, M.D., Senior Instructor in Radiology, St. Louis University School of Medicine, St. Louis, Mo.

**Skin Tests**—their importance in the diagnosis of lung diseases. Herbert L. Mantz, M.D., Tuberculosis Controller, Kansas City, Mo., Consultant in Tuberculosis, Veterans Administration.

**The Five Cardinal Points in the Diagnosis of Clinical Pulmonary Tuberculosis.** George D. Kettelkamp, M.D., Medical Director, Robert Koch Hospital; Assistant Professor of Clinical Medicine, Washington University School of Medicine, St. Louis, Mo.

**Basic Concepts and Objectives in the Treatment of Pulmonary Tuberculosis.** Carl Muschenheim, M.D., Associate Professor of Clinical Medicine, Cornell University Medical College, New York, N. Y. (Dr. Muschenheim also will speak on "Streptomycin in the Treatment of Tuberculosis.")

Among other subjects to be presented are: extra pulmonary tuberculosis, special problems in the management of tuberculosis such as pregnancy, diabetes, syphilis, surgical operations; tuberculous pleurisy with effusion, its management from the standpoint of avoiding subsequent phthisis; public health aspects of pulmonary tuberculosis, mass X-ray surgery, tuberculin testing, general hygiene; the pneumonias, practical points in the diagnosis and management; bronchiectasis; empyema thoracis; bronchogenic carcinoma; mediastinal tumors; mycotic diseases of the lung; the pneumoconioses; use of oxygen therapy, and rare diseases of the lung.

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